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HISTOLOGIC CHANGES IN THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD

VII. ALTERATIONS IN NERVE CELLS

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In a series of studies concerned with pathologic changes in the various cytologic elements of the brain following injuries to the head, of which this study constitutes a unit, we have kept two objectives in view. The first, and perhaps the most important, has been an attempt to explain the residual symptoms which so often persist after an injury to the head. The second, and more academic, objective was an attempt to discover the finer details of such alterations which occur in these various elements as a result of craniocerebral trauma. By a study of such changes it was hoped to shed some light on the biologic behavior of these cells and fibers in response to physical injury. As these studies have drawn to a close, it has become evident that we have been more successful in the attainment of the second than of the first of these objectives. In fact, it may be said that what has been learned regarding the clinical effects of trauma from our pathologic observations has been in a sense a by-product rather than the achievement of a primary objective. Among the other reasons for this situation is the difficulty in the interpretation of the relative seriousness of multitudinous and complex lesions so often found after fatal injury. It is, furthermore, often difficult to sort out the individual effects of the various processes initiated by such an injury. Since these studies have been concerned largely with cases in which death occurred within a few days after injury, one's viewpoint of possible ultimate residual manifestations would necessarily be prospective.

The previous studies in this series to date have brought to light facts which may be stated as follows:

1. After injury there are an increase in volume of the epithelial cells of the choroid plexus and ependyma and an associated increase in cellular vacuolation. The vacuoles themselves are larger than in ordinary circumstances and are increased in average number in the cell.[1] If these changes are indicative of increased secretory activity, as we believe, the source of increased amounts of cerebrospinal fluid, as found clinically, is at least partially accounted for.

2. After death from injury to the head, there is also found an acute swelling of the oligodendroglia cells, particularly those in the white substance of the brain, together with a generalized increase in the number of these cells, the latter being a result of an active direct cell division. The vacuoles in the oligodendroglia cells apparently represented accumulations of fluid within the cell.[2] This change has been interpreted by us as a response to increased amounts of fluid within the nerve tissues (true cerebral edema).

3. There seems to be no specific generalized response of the microglia to injury. Activity of this element depends on actual destruction of tissue, as observed with focal injuries, such as contusions or lacerations.[2] Their action is essentially phagocytic and is provoked by the presence of free blood in the tissues or by disintegrating nerve elements.

4. Likewise, no generalized response of the astroglia elements is found as an acute response to injury. About local contusions and hemorrhages there is a limited response of these elements, as manifested by their proliferation to form a feeble astrovascular scar.[3] We do not believe that these local changes can have any serious effect on cerebral function.

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1. Rand, C. W.: Histologic Studies in the Brain in Cases of Fatal Injury to the Head: I. Preliminary Report, Arch. Surg. **22**:738 (May) 1931. Rand, C. W., and Courville, C. B.: II. Changes in the Choroid Plexus and Ependyma, ibid. **23**:357 (Sept.) 1931.

2. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: III. Reaction of Microglia and Oligodendroglia, Arch. Neurol. & Psychiat. **27**:605 (March) 1932.

3. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: IV. Reaction of the Classic Neuroglia, Arch. Neurol. & Psychiat. **27**:1342 (June) 1932.

The remainder of the studies in this series have been concerned with the parenchymatous elements. These investigations have given a broader insight into the possible causes of the nervous and mental manifestations so commonly observed in patients who have had cerebral injury. The essential observations in these studies are indicated herewith.

1. Cerebral symptoms may be the result of an interruption of nerve fibers, as well as the effect of injury to the cells themselves. The commissural fibers of the brain may be interrupted by the occurrence of small petechial hemorrhages, either within the corpus callosum or in its radiations. Association and projection fibers may also be severed by subcortical traumatic hemorrhage, either primary in origin or secondary to local contusions. The degeneration of nerve fibers originating in portions of the cortex destroyed by contusion explains the atrophy of the white substance and the enlargement of portions of the ventricular system observed consequent to such lesions.[4]

2. The disturbance in the arrangement of the cortical nerve cells may be due to macroscopic or microscopic lesions. The amount of tissue loss depends on the degree of the injuring force and the extent of its concentration. As a rule, the location of gross cortical contusions following traffic accidents is such as not to cause focalizing symptoms other than impairment or loss of smell consequent to subfrontal lesions resulting in injury to, or destruction of, the olfactory bulbs. Nerve cells retain their morphologic identity remarkably close to the margin of the injured area, the local injury destroying these elements only within and in the immediate margin of the lesion.[5]

With these observations in mind, we now turn to the more detailed study of the nature and extent of injury to the nerve cells themselves.

It seemed advisable, because of the clinical manifestations which are to be accounted for on the basis of injury to nerve cells, to consider such post-traumatic alterations as (1) general changes, such as might account for the immediate loss of consciousness after injury (commotio cerebri), and (2) local changes, which are due to compression by dural hemorrhage or to local traumatic lesions of the brain, such as contusions, lacerations and hemorrhages (which explain the occurrence of localizing phenomena).

MATERIAL AND METHODS OF STUDY

The material used in this study was the same as that utilized in previous investigations, viz., blocks of tissue taken from the brain in 39 cases of fatal injury to the head. This material was forwarded to the Cajal Laboratory for our use through the courtesy of Dr. A. F. Wagner and Dr. John H. Schaefer, former coroner's surgeons for Los Angeles County. The bodies had all been embalmed within ten hours after death, and all but five of them within five hours. This prompt fixation was an assurance of well preserved tissue, in which postmortem changes were reduced to a minimum. After their removal from the brain, the blocks of tissue were further fixed in solution of formaldehyde U. S. P. diluted 1 to 10. Sections from selected blocks were prepared with the hematoxylin and eosin stain, Herxheimer's method for fat, Mallory's phosphotungstic acid hematoxylin and aniline blue methods, cyanin and toluidine blue methods for tigroid material and Cajal's reduced silver method and Bielschowsky's silver method for neurofibrils.

GENERALIZED TRAUMATIC ALTERATIONS IN NERVE CELLS

That generalized changes in the nerve cells of the brain occur after injury to the head had long been recognized, although the degree of such changes, their significance in terms of disturbance of function and their possible duration after the initial injury have never been accurately established. While it is too much to expect that all the answers to questions that might be posed are to be found in a study of the cerebral and cerebellar cortex in persons who have died of a craniocerebral injury, it is not unreasonable to suppose that such studies may at least shed a little light in a hitherto dark corner. It is our purpose, therefore, to examine such changes and, after viewing them in the light of experimental investigations which have been made at the hands of several students of the problem, to note their possible connection with the clinical picture which is widely known as "concussion."

A study of the problem in its initial phases brought to light the momentarily disturbing fact that there are two conditions which may be provoked by the general effects of injury and which must be separated if any adequate evaluation of the changes observed were to be made: (1) the immediate effects of injury, which are known as commotio cerebri, or "concussion," and (2) the delayed effects of such an injury in the form of cerebral edema. By utilizing what is known of certain changes in the nerve cells (essentially in the formation of vacuoles) which occur in the presence of edema of the brain, we have tried to distinguish between the changes suggestive of the abnormal collection of fluid in the cell and altera-

4. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: V. Changes in the Nerve Fibers, Arch. Neurol. & Psychiat. **31**:527 (March) 1934.

5. Rand, C. W., and Courville, C. B.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: VI. Cyto-Architectonic Alterations, Arch. Neurol. & Psychiat. **36**:1277 (Dec.) 1936.

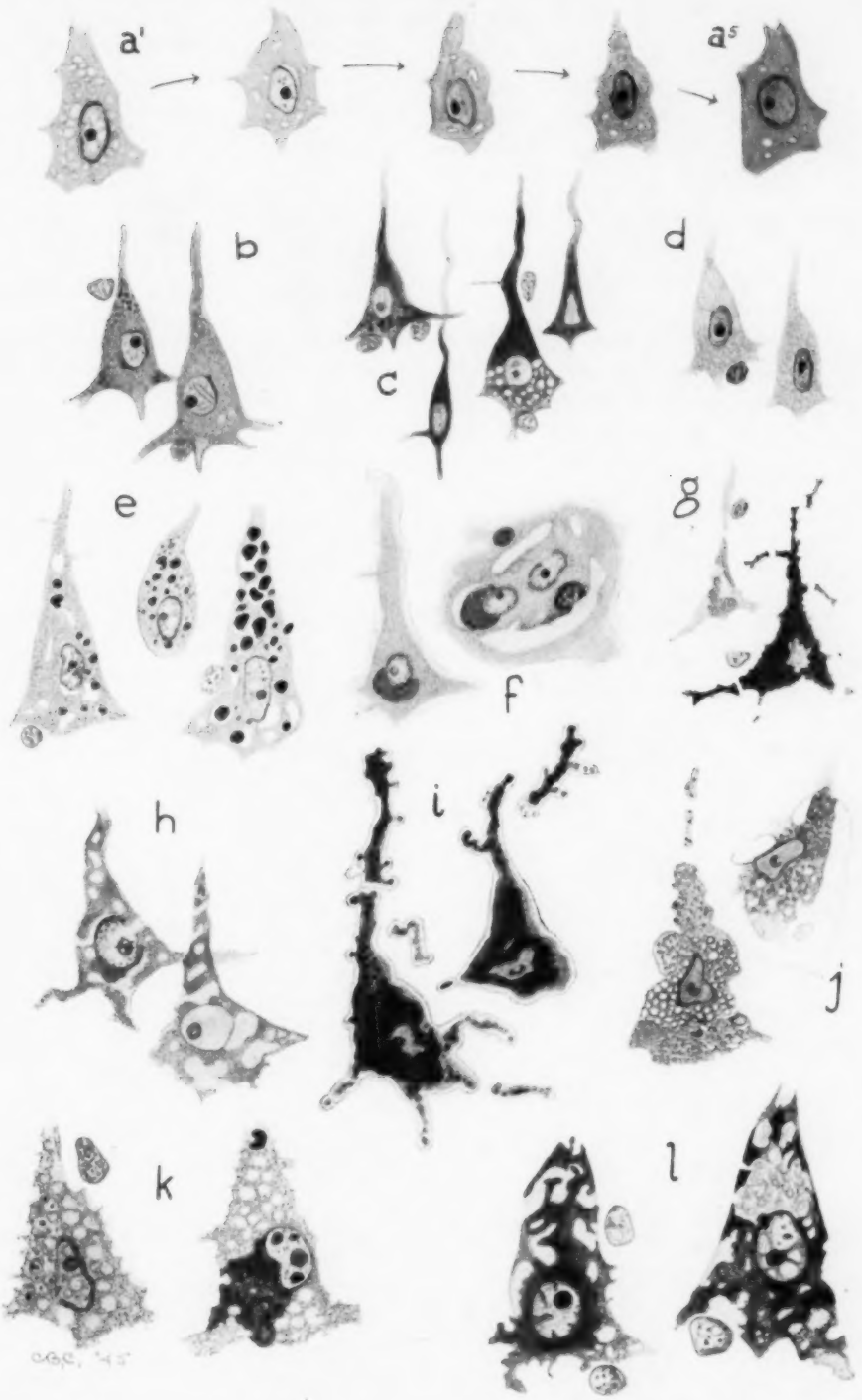

Fig. 1.—Changes in nerve cells of the cerebral cortex incident to trauma. Here, a^1 to a^5 indicate progressive change leading to copper-colored cells; *b*, chromatolysis resulting from concussion; *c*, pyknosis, and, *d*, ischemic change, due to disturbances in circulation near contusions; *e*, pigmentary infiltration adjacent to cortical hemorrhage; *f*, pigmentary atrophy (fatty change), with example of multinucleation; *g*, preliminary and terminal stages of iron encrustation, and *h* to *l*, pronounced cell changes (traumatic degeneration), as shown in various preparations; (*h*, segmentation as a terminal stage of local edema [Bielschowsky-Plein method]; *i*, coarse granulation of neurofibrils [Cajal method]; *j*, cellular disintegration [phosphotungstic acid hematoxylin]; *k*, "vacuolation" of nerve cells [hematoxylin and eosin, aniline blue]; *l*, condensation of chromatin [Bielschowsky-Plein method]).

tions in the amount, appearance and distribution of certain chromatic granules found in the cytoplasm of the fixed nerve cell which have come to be known as Nissl substance, or tigroid granules. Only on this basis can any order be made out of the confusing picture otherwise presented, confusing because the two types of changes are somewhat contradictory.

The possible sources of error in interpreting general changes in nerve cells are manifold. A common mistake is mistaking changes due to poor fixation of tissue which results in postmortem change for true pathologic alterations. Nerve cells in particular are susceptible to improper fixation, and no doubt in the past many minor changes due to this cause have been interpreted as being due to disease. We were fortunate in securing material that had been fixed by embalming within a few hours after death. In most instances this had been done within three or four hours, and in only 5 of the 39 cases was embalming done more than five hours after death. The longest interval between death and embalming was ten hours. When the material was brought to the laboratory, it was promptly fixed in solution of formaldehyde U. S. P. diluted 1 to 10.[6]

One must be constantly on the alert to exclude preexisting disease in attempting to interpret one's observations. Evidences of early parenchymatous syphilis led us to exclude 1 case of the series. Alcoholism, so frequently the cause of the fatal accident, may also change the histologic picture. In senile persons, who are so often run down by automobiles, the brain may show diffuse gliosis and alterations in nerve cells, such as sclerosis and lipoidal degeneration, which must not be confused with traumatic effects. Focal areas of ischemia may be confused with minor contusions. In persons who were comatose many hours before death, dehydration and lack of nutrition may play a part in producing generalized changes. The influence of a high preterminal temperature (hyperthermia) or an elevation of temperature due to associated inflammatory lesions, such as bronchopneumonia, is to be considered. Subclinical meningitis may produce meningeal and cortical changes, the cause of which may escape notice.

While it may seem superfluous to mention it, there is a further danger in misinterpreting the normal variations in the cortical architecture, and even in cellular structure. In some regions, relatively acellular areas may be mistaken for Verödungs by the uninitiated. Normal variations in the cell, such as nucleolar vacuolation, must not be overemphasized. Artefacts incident to or coincidental with the method of preparation may also be misleading at times.

6. In order to assure ourselves that there were no chemicals in the embalming fluid which might interfere with or alter the staining or impregnating processes, an analysis of the fluid was made by the hospital chemist, Dr. Albert Chaney. No heavy metals or strong acids or bases were found to be present. Some coloring material, possibly eosin, and an alkalizing substance, the nature of which was not determined, were present but did not seem to interfere with results obtained with the technical methods. As evidence of proper fixation, we were able to obtain almost uniform success with the various metallic methods used. Individual preparations which were not properly impregnated were discarded. In case of doubt, normal tissues were run through at the same time to act as indicators to insure certainly of results.

Changes in Cortical Nerve Cells Incident to the Shock of Injury (Commotio Cerebri; Concussion).—Perhaps the first observations as to the possible effects of the shock of injury on the cortical nerve cells of the brain were those of Büdinger,[7] who noted that in cases of commotio cerebri there was a tendency for these elements to lose their capacity for staining with ammonia carmine. At this early date, he presumed this change might be accounted for by the effects of *Gehirnerschütterung.* Shortly thereafter, Scagliosi [8] investigated the problem by studying a series of changes in the brains of animals injured by being struck on the head with a hammer. Within a short time after the injury, it was found that the tigroid substance began to undergo lysis in the vicinity of the nucleus, a process which progressively involved the rest of the cell until, at the end of twenty-four hours, the cell had lost its granular substance and had assumed a pale blue, homogeneous appearance. Meanwhile, the cell process had undergone some hypertrophied varicosity and the formation of small club-shaped swellings at their terminations. In repeating this experiment with dogs and monkeys, Jakob [9] found, after six days, widespread changes in the nerve cells (of the brain stem and even of the upper portion of the spinal cord, as well as of the cerebral cortex) in the form of swelling and intensification of the staining of the tigroid material, at times with early chromatolysis, eccentration of the nucleus and, occasionally, neuronophagia. These alterations resembled the condition known as acute nerve cell disease described by Nissl, and it was assumed that the changes were reversible.

Essentially the same alterations were reported by de Lisi,[10] who studied changes in the cerebral nerve cells in chickens and dogs. According to this investigator, the changes were not constant but, when present, consisted in chromatolytic and

7. Büdinger, K.: Ein Beitrag zu der Lehre von der Gehirnerschütterung, Deutsche Ztschr. f. Chir. **41**:433-444, 1895.

8. Scagliosi, G.: Ueber die Gehirnerschütterung und die daraus im Gehirn und Rückenmark hervorgerufen histologische Veränderungen, Virchows Arch. f. path. Anat. **152**:487, 1898.

9. Jakob, A.: Experimentelle Untersuchungen über die traumatischen Schädigungen des Zentralnervensystems (mit besonderer Berücksichtigung der Commotio cerebri und Kommotionsneurose), in Nissl, A., and Alzheimer, F.: Histologie und Histopathologie. Arbeiten über die Grosshirnrinde, mit besonderer Berücksichtigung der pathologischen Anatomie der Geisteskrankheiten, Jena, G. Fischer, 1913, vol. 5, p. 182.

10. de Lisi, L.: Sulle alterazioni del sistema nervoso centrale degli animali, sottoposti a commozione cerebrale, Atti d. Cong. d. Soc. ital. di neurol. **4**:169-174, 1914.

nuclear alterations, which (in agreement with Jakob) involved the cells in the brain stem and the upper portion of the spinal cord, as well as the cerebral cortex. De Lisi stated the belief that these effects were due either to the shock of the injury or to some vasomotor effect (constriction) resulting therefrom.

This study by de Lisi is of interest, for there has been a recent tendency to compare these effects of electric shock with those of concussion (Hassin [11]). Approaching the problem from a slightly different angle, Langworthy [12] studied the changes in the cortical ganglion cells after electric shock. In cases of severe injuries, with immediate death, he found that the nuclei were shrunken and that they stained deeply, so that the chromatin threads and nucleolus could no longer be distinguished. With less severe injuries the cell body was observed to be shrunken, with corresponding enlargement of the perivascular space. There was a decrease in the amount of Nissl's substance, which appeared flaky and coarsely granular. The cytoplasm stained a uniform deep color. In a study of a series of these cases, it was found that the tigroid substance gradually reformed, being first restored either in the periphery of the cell or in the zone about the nucleus.

In their experimental studies on the effects of explosions, Mairet and Durante [13] found that the nerve cells seemed unaltered as an immediate effect but that after five to nine months some atrophic changes in motor nerve cells were noticed, together with an alteration in the normal columnar arrangement of such cells. Their observations seem to indicate that there is a fundamental difference between the effects of concussion due to head injury and those due to explosions.

Osnato and Giliberti [14] noted an unevenness of the staining qualities of the pyramidal nerve cells of the cortex and the Purkinje cells of the cerebellum after injuries to the human brain and found considerable loss of tigroid material, especially in the latter elements. Ramón y Cajal [15] had observed that experimental commotio cerebri resulted in "certain nutritive disorders" of the nerve cells in the form of such alterations as vacuolation and chromatolysis. Neubürger [16] observed changes in the nerve cells (ischemic change) of the hippocampus in cases of gunshot wound of the brain and some alterations in the cells of the cerebellar cortex as well. He attributed these widespread variations, however, to circulatory effects and not to the direct effects of injury. Minkowski [17] concluded that the generalized chromatolysis and changes in the nucleus and protoplasm which are found after injury, which were described by previous observers and verified by him are to be accounted for on the basis of commotio cerebri.

Dissatisfied with the conclusion that the changes described by previous investigators were the effect of "pure" concussion, Windle, Groat and Fox [18] and Groat, Windle and Magoun [19] repeated the classic experiments on guinea pigs and monkeys. They found chromatolysis of the nerve cells of the vestibular nuclei and of the reticular formation of the brain stem and shrinkage of some of the large cortical (precentral) pyramidal cells (or sclerotic change). It is obvious that these investigators have only segregated the minor alterations in transitory states from more enduring ones and have further contributed to the highly artificial conception of concussion as a purely momentary clinical state.

In our studies in the cases of injury to the human brain, a number of general changes were observed which might well be considered as manifestations of commotio cerebri, agreeing as they do with the experimental observations already cited. In addition to chromatolysis, which seemed to be the most common change noted, other alterations in the nucleus, particularly in the chromatin material, have been observed.

11. Hassin, G. B.: General Pathological Considerations in Brain Injury, in Brock, S.: Injuries of Skull, Brain and Spinal Cord, ed. 2, Baltimore, Williams & Wilkins Company, 1943.

12. Langworthy, O. R.: Histological Changes in Nerve Cells Following Injury, Bull. Johns Hopkins Hosp. **47**:11 (July) 1930.

13. Mairet, A., and Durante, G.: Contribution à l'étude expérimentale de lésions commotionelles, Rev. neurol. **35**:97 (Feb.) 1919.

14. Osnato, M., and Giliberti, V.: Postconcussion Neurosis: Traumatic Encephalitis: A Conception of Postconcussion Phenomena, Arch. Neurol. & Psychiat. **18**:181 (Aug.) 1927.

15. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928, vol. 2, pp. 631-713.

16. Neubürger, K.: Akute Ammonshornveränderungen nach frischen Hirnschussverletzungen, Krankheitforsch. **7**:219 (June) 1929.

17. Minkowski, M.: Klinisches und pathologisch-anatomisches zur Frage der traumatischen Hirnschädigung und ihrer Folgezustände, Schweiz. med. Wchnschr. **60**:701 (July 26) 1930.

18. Windle, W. F.; Groat, R. A., and Fox, C. A.: Experimental Structural Alterations in the Brain During and After Concussion, Surg., Gynec. & Obst. **79**:561 (Dec.) 1944.

19. Groat, R. A.; Windle, W. F., and Magoun, H. W.: Functional and Structural Changes in the Monkey's Brain During and After Concussion, J. Neurosurg. **2**:26 (Jan.) 1945.

Chromatolysis: This condition, which has been consistently reported as one of the general changes in the nerve cells as a result of trauma to the head, has also been observed by us in our study of the effects of injury on the human brain.[20] In a case in which the person had been killed outright, no change was observed in the amount, character or distribution of the tigroid substance. In another case, with a survival period of about an hour, the tigroid substance was coarsely granular. After one and a half hours, however, this substance was found to be absent in a ring about the nucleus in some of the cells, a change which was still more marked at the end of two and a half hours. No further change was noticed after twelve hours, but after twenty-four hours (in a case with a survival period of thirty-one hours) the cortical ganglion cells were generally agranular; in the remaining few cells which contained this material it was irregularly distributed (fig. 2). This was also true in 2 cases with survival periods of three and a quarter and three and one-half days. At the end of six days, however, some cells were found which showed only a perinuclear loss of chromatic substance, an observation which indicates that there is some variability in the rapidity and extent of loss of tigroid substance. This variability is likely dependent on the degree of shock of the original injury, on the character and degree of other traumatic effects and on what occurs in the interval between the injury and the time of death. After fourteen days little granulation of the cells was found to be present, and after twenty-one and thirty-nine days' survival practically all the cells remained agranular.

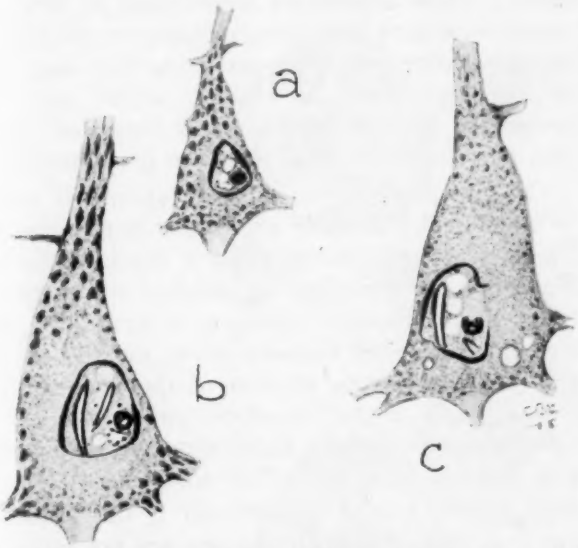

Fig. 2.—Chromatolysis incident to commotio cerebri (concussion), showing (*a*) early perinuclear loss of tigroid substance; (*b*) persisting ring of Nissl granules, with nuclear eccentration and distortion and folds in the nuclear membrane, and (*c*) agranular cell with vacuolation of the cytoplasm and nucleus (edema) and rupture of the nuclear membrane.

There are some alterations in the Nissl substance which have been described in cases of experimental cranial injury which we have not been able to verify in the human specimens which we have studied. For example, de Luzenberger[21] described the collection of tigroid material at one pole of the cell after striking animals repeatedly on the head with a hammer. This was most evident in the region of the injury and should perhaps be considered as a more local rather than a general effect. Ingvar[22] described a similar and more general change in the nerve cells after centrifugation of the head and brain. These specific types of alteration have been accounted for on the basis of a difference in the specific gravity of the tigroid substance (whatever be the true nature of this material) and that of the cytoplasm of the cell in general. While certain theoretic situations affecting the head of man in the process of injury might be postulated, we have not been able to establish the presence of such alterations in the specimens which have come to our attention.

On the basis of these observations in cases of injury to the human brain, one may conclude that the shock of severe injury is manifested within two hours by a loss of tigroid material, which loss is first evident in the perinuclear zone. This process seems to proceed fairly rapidly, for after twelve hours it is widely present and after twenty-four hours one may find most of the cells affected by loss of this granular substance. However, even after several days, perhaps in persons who have not been so seri-

20. It is aside from the purpose of discussion in this connection to go into the various arguments which have been advanced as to the nature, or even the reality, of this substance, which has been variously known as Nissl or tigroid bodies and chromophil or chromidial substance. Contrary to the opinion of some investigators, it has been demonstrated in the living anterior horn cell of man. But in general it is not found in the state of granulation in most circumstances, and it has therefore been assumed to be the coagulation product of fixation, in which certain other iron-containing granular elements of protein character are precipitated. Be all this as it may, its uniform presence in normal circumstances and its dissolution under many pathologic conditions give one something to conjure with in the interpretation of neuropathologic states, even though the results fall far short of the original high hopes that its discoverer, Nissl, had for it.

21. de Luzenberger, A.: Su d'una speciale alterazione delle cellule gangliari prodotta da trauma, Neurol. Centralbl. **17**:363, 1898.

22. Ingvar, S.: Centrifugation of the Nervous System: An Investigation of Cellular Changes in Commotion, Arch. Neurol. & Psychiat. **10**:267 (Aug.) 1923.

ously injured but who have died of some intercurrent cause, granulation may still be present in many individual nerve cells. In the cases with longer survival period (two weeks and more), granulation is poorly represented, if present at all. This may indicate that reversal of this change may take place very slowly or that other factors, such as intercurrent infection (meningitis, pneumonia) or occurrence of interval hemorrhages, may act to continue the process which the original shock of injury has begun. While one must be cautious in interpreting alterations in the tigroid material (since so many possible disturbing factors are present in these cases of human injury), a study of this material seems to verify the experimental observation of loss of this substance as a general effect of cranial injury.

Alterations in the Neurofibrils: This feature has not been noted as a general thing in the reported studies on experimental injury. Therefore, there is nothing with which to compare our observations in cases of human injury. This phase of the subject (commotio cerebri) was entirely ignored by Cajal, whose monumental studies on neurofibrillar reactions to local injury are of great help in the interpretation of injuries of the human brain. From our studies, true alterations of the intracellular neurofibrils of nerve cells in general, as demonstrated by the Bielschowsky method, are limited in degree. In 1 case after twelve hours some tortuosity and occasional fragmentation of these elements were observed, but after fourteen days no evidence was seen of any alteration of neurofibrils in nerve cells distant from the local injury. With the use of reduced silver, however, an entirely different picture is presented, which has led us to conclude that the structures demonstrated by these two methods are not identical.[23] Even in the cortex of persons killed outright some granulation of these elements were made out, a change which became increasingly apparent within the first few hours after craniocerebral trauma. In this respect, the small pyramidal cells seemed to suffer from the effects of shock more than the medium-sized or large ones. The character of the changes observed suggested that the neurofibrils underwent a process of coarse or fine granulation as an immediate effect if the shock was severe (persons with short survival periods), while with less severe injuries a slower process of change was noted—varicosities and fusiform enlargements were observed, apparently as preliminary changes leading to segmentation and coarse and fine granulation of these structures. These alterations were found as late as twenty-one days after severe injury to the head, an observation which suggests that they may be of the nature of a change which permits reversible reaction, but just how long this reaction may be delayed has not been determined.

On the basis of these observations, it may be concluded that some alterations in the neurofibrils occur as a general effect of cranial trauma. But since the Bielschowsky method shows relatively few structural changes, it may also be concluded that the reduced silver method demonstrates only some portion of these elements, perhaps only a thin envelope, rather than the essential element of the fibril, whatever its nature and function may be. How long these alterations persist in the injured cell is not known, but it is clear that such changes are not incompatible with a living cell and are very likely reversible in character.

Nuclear Changes: These changes, while not marked or perhaps of great importance, are nevertheless interesting. Whether vacuolar changes in the nucleus and nucleolus are to be considered as evidence of edema or of some other regressive process is not entirely clear, but they will be described in connection with other alterations which are suggestive of edema. Within two hours after severe injury to the head, the nuclei of the cortical nerve cells may assume an eccentric position in the cell; their contours become irregular, and folds in the nuclear membrane are found, which suggest some degree of shrinkage of this structure. This membrane may also show considerable variation in its thickness. With longer survival periods, the nucleolus also becomes eccentric and may be found lying against the nuclear

23. Since the majority of sections studied for possible alterations in nerve cells were prepared by both the Bielschowsky and the Cajal method for neurofibrils, we have had opportunity to compare the two pictures resulting therefrom. It soon became obvious that the two methods were demonstrating different parts or elements of the neurofibrils. What appeared to be a perfectly normal neurofibrillar apparatus with the Bielschowsky method disclosed many and varied alterations with reduced silver. It has therefore been assumed that the Bielschowsky method gives one a better impression of the functional state of the cell. However, the consistent picture of the reduced silver method of Cajal must have some structural significance, even though we are unable to translate these appearances into physiologic counterparts. It appears that the reduced silver method may demonstrate a fine sheath of the individual neurofibrils, one which is sensitive to pathologic change. The Bielschowsky method, on the other hand, discloses the true element, which is much more resistant to abnormal processes. That there may be some other, and more correct, interpretation of the phenomena is well recognized.

membrane. Of much greater interest are the changes in the contained chromatin material.

Alterations in Chromatin Material: These changes occur as a rather unusual general effect of cranial injury. In normal circumstances the chromatin of the nucleus of a nerve cell is rather finely divided and fairly evenly distributed. Within an hour or two after injury the chromatin material is found to be arranged in chain-like strands, and after twenty-four hours it is found to have assumed a coarser quality, forming either maplike patterns or agglutinations adherent to the nuclear membrane. It is not until about two weeks have elapsed that certain bizarre arrangements of this material are to be observed. While such alterations are found in the vicinity of local traumatic lesions, they also occur apparently as a general change in these circumstances. Such changes persist for as long as thirty-nine days, but how much longer is not known. Some of the interesting forms found after the aforementioned interval are shown in figure 3. The individual masses, of various sizes and shapes, may form a ring about the nucleolus, often forming a border to a perinuclear vacuole under these conditions. In other cells, the various individual masses may be connected through elongated masses of this substance or through the medium of chromatin threads. These patterns are usually found in the vicinity of the nucleolus, often entirely enveloping this structure. The significance of this change as a response to injury is not known.

Other General Changes: Other alterations in the cortical nerve cells seem to be incidental and are perhaps due to some undetermined local effect not otherwise evident. Among the occasional observations in cases of human injuries have been described focal vascular lesions with ischemic change in the nerve cells of the hippocampus (Neubürger [16]) as a consequence of gunshot wounds of the brain. We have noted occasional neuronophagia, irregularities in cell contour, rupture of the nuclear membrane and pyknotic change.

Alterations in the Purkinje Cells of the Cerebellum.—Evidently to be accounted for only as a general effect of trauma (commotio cerebri) are certain alterations in the Purkinje cells of the cerebellum, which are perhaps best described separately, although the individual changes are not greatly different in character from those previously described as being found in the pyramidal cells of the cerebral cortex. Somewhat paradoxic in their behavior are these cells (which Cajal [15] described as showing most energetic and prompt reaction to local injuries), for they are rather easily affected by most noxious processes. This is also true of their response to concussive effects. Within an hour after severe cranial injuries the tigroid substance in some of these elements may be almost completely absent. In 1 case with a survival

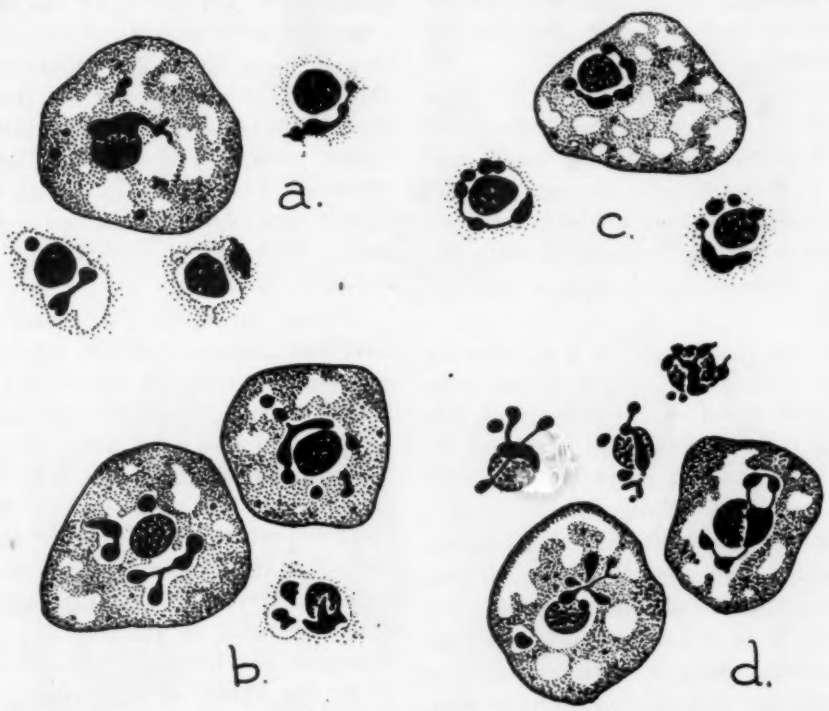

Fig. 3.—Peculiar condensations of nuclear chromatin incident to commotio cerebri (concussion), showing (*a*) agglutination masses, (*b*) ring forms, (*c*) multiple masses and (*d*) mass-fibril combination patterns.

period of sixteen hours, the tigroid material was largely dissolved, and after thirty-one hours what little substance was still present was found in the upper pole or at the periphery of the cell. After forty-eight hours the cells were completely agranular and remained so for an undetermined length of time.

The neurofibrillar elements, demonstrated by the reduced silver method, were also definitely affected. These elements may be found to be deficient, either in the peripheral (hirudiform change) or the central portion of the cell, or the entire structure may be coarsely or finely granular. The presence of normal structures as demonstrated by the Bielschowsky method, while reduced to granulations as shown by the reduced silver method, is further evidence of the fact that these two methods demonstrate different structures.

It may be concluded, therefore, that in man the Purkinje cells of the cerebellum reflect the general effects of trauma in much the same manner as do the pyramidal cells of the cerebral cortex. These changes, too, are probably reversible and represent a transitory physical state the physiologic equivalents of which have as yet not been determined.

Summary.—From the results of a number of reported experimental investigations, it has been shown that a generalized chromatolysis of the cortical ganglion cells is the usual response to cranial injury. It has been assumed that this reaction is due to the shocking effects of the injury (Minkowski) and that these alterations probably correspond with clinical manifestations which have come to be known as concussion, or commotio cerebri. It is of interest to know that we have noted similar changes in cases of injury to the human brain, as well as alterations in that portion of the neurofibrillar apparatus demonstrated by the reduced silver method, together with changes in the nucleus (irregularities in contour, folds in the nuclear membrane, eccentration of the nucleus and nucleolus and alterations in the size of the chromatin particles, as well as in their arrangement).

While all this is true, some details of the problem are not entirely clear. In the first place, the brains studied in this investigation were from persons who succumbed to the effects of their injuries within a relatively short time. Certainly the condition in patients who die within a few days does not represent the situation present in persons who suffer a momentary loss of consciousness after cranial injury. Among the patients with longer survival periods, however, there are some who doubtless represent the group of patients with moderate injuries and who frequently recover. Even in this group the changes here outlined were present. Such alterations may therefore be considered as basic for at least moderate injuries.

But the period of unconsciousness in the latter group was often relatively short, and complete recovery from any general symptoms would have been expected had not complications arisen. Therefore, one should not attempt to account for temporary loss of consciousness, with restoration to the normal state in that respect within a few hours, on the basis of alterations in the nerve cells which persist for at least a month, or over. In short, there is as yet no exact parallel in man between the generalized alteration in nerve cells and the relatively acute aspects of concussion. But there is a possible basis for understanding certain of the subacute disturbances in the function of the central nervous system, especially in the psychic realm, which tend to clear up within a few months. Therefore, one must be at least hesitant in describing all untoward subjective symptoms which follow "concussion" as purely functional in character.

Changes in Nerve Cells Incident to Traumatic Cerebral Edema.—While the condition known as traumatic cerebral edema has been known for a long time, it has been only recently that any information has been available as to the possible changes in nerve cells that might follow the development of this state. In fact, present opinions on the subject are the result of the merger of three separate lines of histologic investigation. Over half a century ago, Macpherson [24] noted vacuoles in the cortical nerve cells after injury to the human brain, which he concluded to be the result of concussion. He expressed the belief, further, that these vacuoles were the direct result of some vascular state which affected the nutrition of the cells and which resulted in a breaking down of the albuminous substance into fat. While a definite effect on the physiologic state of the cell was assumed, the vacuole itself was not considered to be of fluid nature and was not thought of in relation to traumatic edema of the brain. Since that time, vacuolation of nerve cells has been reported in cases of experimental injury, usually produced as the result of direct force, in which cerebral edema is a minimal condition. Moreover, these vacuolated cells were evidently a local and not a generalized response (Scagliosi [8] and others). While such vacuolation has frequently been re-

24. Macpherson, J.: Vacuolation of Nerve-Cell Nuclei in the Cortex in Two Cases of Cerebral Concussion, Lancet **1**:1127 (May 21) 1892.

ferred to by subsequent investigators, the possible significance of this somewhat isolated observation made in cases of injury to the human brain has been generally overlooked. Cajal [15] mentioned the possibility that vacuolation of nerve cells might be the result of commotio cerebri, as well as a general effect.

Meanwhile, attention was directed to a type of cell change which was considered to be associated with certain circulatory changes (*Wasserveränderung* [Nissl], *ödematöse Ganglienzellveränderung* [Jakob]). This type of cell change was found as an agonal effect or with extreme cerebral edema ("wet brain"), such as might follow heart failure. It was also noted at the cells did occur, these elements were rather resistant to the influence of excess fluid in the nerve tissue. These observations were verified by Ferraro,[26] who was able to demonstrate the presence of large vacuoles in the cortex of hydrated rabbits, establishing beyond any question the fact of edematous change as a possibility in the presence of increased amounts of fluid in the tissue of the brain. Reid [27] demonstrated similar changes in nerve cells with this method, accentuating the degree of cellular vacuolation by removing the skull cap and opening the dura of his experimental animals before injecting the hypotonic solution. These various degrees of alteration are due to edema (fig. 4).

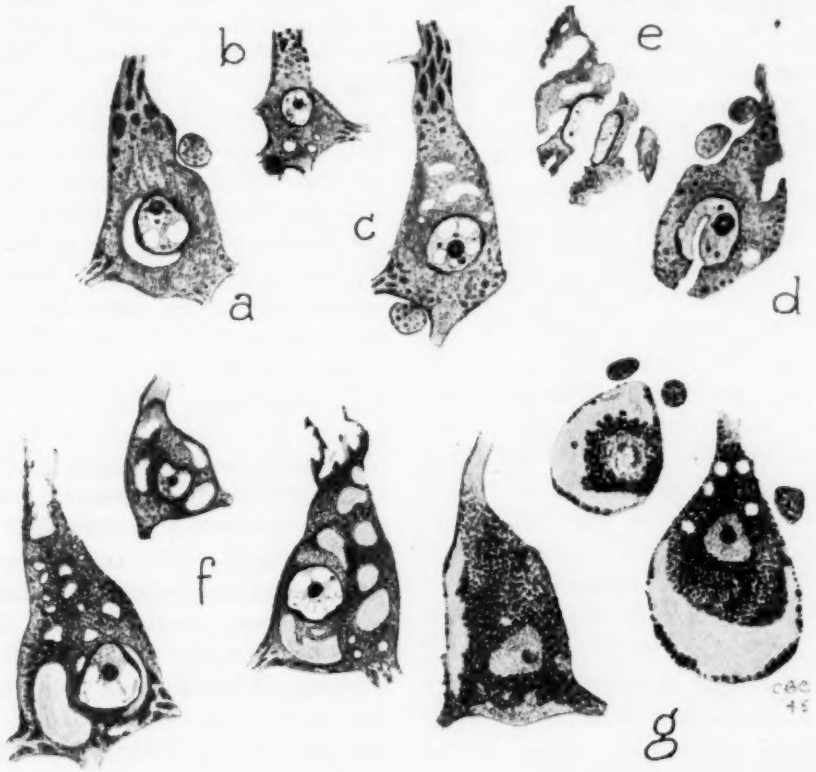

Fig. 4.—Cellular alteration incident to traumatic cerebral edema. Here, *a* to *e* indicate changes seen after injury to the human brain (*a* to *c*, general changes; *d* and *e* changes about local traumatic lesions); *f* and *g*, changes after experimental hydration of the brain (*f*, cellular vacuolation [after Ferraro [26]]; *g*, formation of cellular fluid lakes after removal of the skull and dura [after Reid [27]]).

margin of such vascular lesions as hemorrhage or infarction.

The third line of investigation which was to show that this type of cell change might also be found as a traumatic effect was introduced by Weed,[25] who studied the effects on the brain of intravenous injection of hypotonic solutions in experimental animals. This investigator observed that while vacuolar changes in the nerve

The fact that vacuolation of nerve cells takes place as a consequence of cranial trauma (Macpherson), the occurrence of edematous change as a special type of change in nerve cells (Nissl, Jakob) and the association of this change with hydration of the brain, therefore, established the possibility that vacuolation as a type of change in nerve cells might well occur as a consequence

25. Weed, L. H.: The Effects of Hypotonic Solutions upon the Cell-Morphology of the Choroid Plexuses and Central Nervous System, Am. J. Anat. **32**:253 (Sept.) 1923.

26. Ferraro, A.: The Reaction of the Brain Tissue to Intravenous Injection of Hypotonic Solutions, J. Nerv. & Ment. Dis. **71**:129 (Feb.) 1930.

27. Reid, W. L.: Cerebral Oedema, Australian & New Zealand J. Surg. **13**:11 (July) 1943.

of traumatic cerebral edema. Since the nerve cells were found to be resistant to the effects of an excess of fluids in the nerve tissues (Weed [25]) in cases of traumatic cerebral edema of the generalized type (Courville [28]), it was to be expected that such alterations would be of minor character, a conclusion shared by Reid,[27] and would occur in the form of vacuoles which were filled with fluid.[29]

In our investigation of the general effects of injury to the human brain, vacuolation of nerve cells, not otherwise accounted for, was observed within an hour or two after injury. These vacuoles were first noted in the nucleus and the nucleolus. The nuclear vacuoles, at first small, increased in prominence with the lapse of time, until the occurrence of multiple vacuolar spaces resulted in a maplike design in the nuclear chromatin. The vacuoles in the nucleolus were usually small and droplike, at times two or three being found in this structure.

After twenty-four hours, in cases of definite cerebral edema, one may find small, semilunar clear spaces about the nucleus (perinuclear vacuoles). These may be overlooked unless carefully sought for in routine preparations. By this time, however, the pericellular and perivascular spaces may be notably enlarged, suggesting an excess accumulation of fluid in the brain and thus leading one to search for these more specific alterations incident to a disturbance of fluid balance within the cell. Such changes have been observed in typical conditions after three and a half days. Vacuoles in the cytoplasm do not appear as a rule and, if present, tend to occur after several days have elapsed. They may be found as long as several weeks after the injury. These cytoplasmic vacuoles are small and sharply defined and usually occur in the basilar portion of the cell, in the region of the nucleus.

"Edematous Change" and Alterations in Nerve Cells Associated with Cerebral Edema: Nerve cells showing edematous change are slightly smaller than normal and contain a shrunken irregular, hyperchromatic nucleus; they have no typical tigroid granules but show irregular masses of chromatic material, which stains deeply. On the other hand, the nerve cells which contain the vacuolar spaces aforementioned are pale and agranular, and their nuclei, likewise, are somewhat lighter in color, owing to the presence of nuclear vacuoles which scatter the granular material. Therefore, the changes in nerve cells incident to cerebral edema are not entirely synonymous with the "edematous change of nerve cells." As has already been shown, there are two factors at work in the production of these generalized changes—the shock of the injury (commotio cerebri) and a disturbance in tissue fluid balance. The end product of these two processes is the cell change previously described, resulting in an agranular, pale cell in which the nucleus is shrunken and eccentric and fluid vacuoles are sometimes found, both in its cytoplasm and in its nucleus.

28. Courville, C. B.: Structural Changes in the Brain Consequent to Traumatic Disturbance of Intracranial Fluid Balance, Bull. Los Angeles Neurol. Soc. **7**:55 (June) 1942.

29. Courville, C. B.: Pathology of the Central Nervous System, ed. 2, Mountain View, Calif., Pacific Press, 1945.

Summary.—The nerve cells of the cerebral and the cerebellar cortex may be generally affected as a result of injury, in contrast to certain other alterations which occur in response to a local traumatic lesion. As has just been indicated, these changes consist of a combination of two effects—that of shock of injury, which produces unconsciousness, and a disturbance in the fluid balance in the cerebral tissues, which has come to be known as traumatic cerebral edema. The end result, so far as the changes in the nerve cells are concerned, is dependent on the relative effects of these two processes. The shocking effect of the injury appears to be responsible for loss of the tigroid substance from the cell, a process which begins usually in the perinuclear region; granulation of that part of the neurofibrillar structure demonstrated by the reduced silver method; shrinkage of the nucleus, with assumption of an irregular shape and the formation of folds in the nuclear membrane, and, ultimately, peculiar agglutination and pattern formation of the chromatin substance. These changes are evidently reversible, at least in their minor stages. The cell changes are probably to be found long after the patient has recovered consciousness; so they cannot be said to be responsible for the acute manifestations of concussion. While there is no known way in which the physiologic counterpart of these structural changes can be evaluated clinically, it is possible that they may account for certain of the psychic alterations which so often occur after commotio cerebri. At any rate, they furnish some reason for caution in describing all such manifestations as being purely functional in character.

CHANGES IN NERVE CELLS DUE TO LOCAL POST-TRAUMATIC LESIONS

Local traumatic lesions which might be responsible for change in nerve cells may be divided into two categories: (1) lesions causing pressure on some region of the cerebral cortex such as depressed fracture or extradural and subdural hemorrhage, and (2) lesions causing destruction of the cortical substance proper, such as contusion and laceration of the cortex. Because the

experimental observations in cases of these two types of lesions have been recorded separately, and because from a clinical standpoint the two situations are quite distinct, it has seemed advisable to consider each as an individual entity.

Compressive Lesions.—Under this heading will be considered only those lesions which cause pressure on the cerebral cortex without producing actual structural disorganization or damage. Thus, if a depressed fracture results in laceration of the underlying cortex, one is dealing with something else than compression. This distinction is important, for without physical damage one has reason to believe that changes in the nerve cells which might be due to the compression are reversible.

Destructive Lesions.—A different situation exists so far as contusions and lacerations are concerned. Within the area of destruction it may be assumed that all parenchymatous and interstitial elements are alike destroyed. Moreover, at the margin of the lesion there occurs a zone of destruction in which the elements are immediately killed, although their disintegration may be delayed for some time, owing to "preservation," a process which will subsequently be described. . This zone of disintegration may widen to some extent as time goes on, but in case of contusion there soon becomes apparent a fairly sharp margin to the lesion. In lacerations, however, the margin between the preserved tissue and the zone of destruction is not so sharply drawn, and pockets of nerve tissue may continue to undergo dissolution for a considerable interval of time. Adjacent to the zone of destruction is a second zone, in which the elements may sustain physical damage and yet survive in a crippled or "mummified" state for a considerable interval of time. Still more distal is a zone of reversible reaction in which the nerve cells, as well as other elements, are not so seriously injured but that they can be restored to normal structure, and perhaps to normal function.

Since alterations due to compression are the least important and, by deduction, the least evident, these changes will be considered first. Such alterations are evidently reversible in character, in contrast to the destructive, or necrobiotic, changes which are to be expected in case of contusions or lacerations.

CHANGES IN CORTICAL NERVE CELLS DUE TO LOCAL COMPRESSION

Most of what is known about the effect of local compression on the cortical nerve cells has been learned from experimental studies on animals. This is an obvious necessity, since the majority of human patients with local compression after injury do not succumb to the lesion. Apparently, in those instances in which death has taken place from some associated lesion, a critical pathologic study of changes in nerve cells under the compressing lesion has not been made. In the early days of experimental histologic examination, this subject seemed to be rather popular, and one finds that a number of notables investigated the question experimentally — von Bergmann, Adamkiewicz, Albert, Ziegler and Kahler. Some of their studies, however, were directed toward alterations in the spinal cord rather than in the brain. One of the first critical studies was that of Neumayer,[30] who studied the changes in the cortex of rabbits after compression incident to a lead plate introduced between the cranial vault and the dura. This investigator divided the changes that followed into four periods: (1) In the first period (six to thirteen hours) no degenerative changes were found, although there was loss of the chromatic material in the cytoplasm of the nerve cell; (2) in the second period (after twenty-four hours) degenerative changes became apparent in the nerve fibers of the tangential fiber layer, as well as in the layer of the small pyramidal cells; (3) in the third period (two to ten days) proliferation of the interstitial elements "at the expense of the nerve cells" was observed, while (4) in the fourth period (ten to sixty days) a progressive disintegration of the nerve elements was noted.

Roncali [31] repeated this work on dogs; and he, too, classified the changes observed into four periods. After twenty-four hours, he observed that there was an initial degeneration of the nerve cells and fibers of the superficial layers of the cortex, with deformation and decoloration of the nerve cells. Up to five days, changes in the nerve cells, from minor chromatolytic alterations up to complete destruction, were found in the molecular layer and the superficial and middle layers of Golgi. From ten to fifteen days, alterations in the nerve cells of all layers and to all degrees were in evidence. After twenty days, disintegration of the nerve elements was progressive.

In what is perhaps one of the first studies on the effects of pressure on the cortex in cases of extradural and subdural hematoma, Ewing [32] found that beneath the area of pressure the nerve cells had lost their tigroid substance in whole or in part, the loss being first evident in the perinuclear zone and the peripheral zone being the last to show traces of them. Essentially the

30. Neumayer, L.: Die histologischen Veränderungen der Grosshirnrinde bei localem Druck (Experimentalstudie aus dem histologischen Laboratorium des pathologischen Institutes zu München), Deutsche Ztschr. f. Nervenh. **8**:167, 1895-1896.

31. Roncali, D. B.: Intorne alle alterazioni nella fina tessitura dell' sostanza nervosa dell' encefalo conseceture delle compressione sperimentale, Arch ed atti d. Soc. ital. di chir. **12**:144, 1898.

32. Ewing, J.: Studies on Ganglion Cells, Arch. Neurol. & Psychopath. **1**:1, 1899.

same changes were recorded in a case of recent extradural hemorrhage, as well as in 3 cases of chronic subdural hematoma.

With the aid of his reduced silver method, Cajal [15] studied the effects of compression on the cortical nerve cells in experimental animals. In addition to chromatolytic changes and some degree of vacuolation, he observed after six hours of cerebral compression what he designated as a "hypertrophic neurofibrillar state," manifested by local thickening and intense stainability of these elements. This change was apparently only transitory, for it persisted no longer than two days. A more typical change was a fusiform state of the fibrils, which became evident from ten to twenty-four hours after compression and also disappeared in two days. A "state of discontinuous or granular reticulum" was also observed in his cases, a condition in which granulation of the somatic reticulum was observed. It should be pointed out that these complex changes in the neurofibrillar structures were not typical of compression, for they were also found in destructive lesions of the cortex. We have observed similar changes in nerve cells of the human brain at the margins of contusions, as will shortly be described.

A more recent experimental study on changes due to cortical compression is that of Ugurgieri.[33] He found that in rabbits the chromatic substance showed the earliest changes with compression of the brain by a complex mechanism. Neuronophagia was occasionally observed, as were sclerotic (pyknotic) changes, and at times atrophic alterations in the nerve cells. These observations did little more than confirm those of earlier investigators.

In this series of cases we have had little opportunity to study the alterations in nerve cells which might be considered to be due to pressure alone. In 1 case of subdural hemorrhage the nerve cells beneath the hemorrhage were found to be agranular; the nucleus was eccentric in many cases, and dislocation of the nucleolus (eccentration) was also evident. However, since similar changes were rather widespread, incident perhaps to commotio cerebri or an associated condition, one could not say with certainty that these cell changes were actually due to local pressure.

In a case, not of this series, studied by one of us (C. B. C.), a patient had sustained a local depressed fracture of the left parietal region of the skull. An electroencephalogram had been made, and abnormal (slow) waves were found coming from the region of the depression. The patient died of an intercurrent condition, and at autopsy no gross change in the cortex beneath the depression could be found. A block of tissue was taken from this area and another (for comparison) from a corresponding area in the opposite parietal lobe. The nerve cells in the cortex subjected to compression showed a notable loss of tigroid substance as compared with the normal cortex on the opposite side; minor nuclear alterations were also observed. Whether these changes were to be accounted for by continued pressure or by a minor, but not evident, contusion at the moment of impact, as Naffziger and Glaser [34] averred, is of course debatable.

In conclusion, one must state that local pressure on the cortex can produce minor, and in most instances reversible, changes in the affected nerve cells. These changes consist in progressive loss of tigroid substance and eccentration of the nucleus. If the pressure is of considerable degree (as has been demonstrated in the animal experiments), actual degenerative changes in the nerve cells may take place. It may be that such changes are to be accounted for by an interference with their regional blood supply rather than by any mechanical effect of the pressure. From a clinical standpoint, it is rather unlikely that such degrees of pressure occur with any frequency. As Naffziger and Glaser [34] have shown experimentally, depressed fractures are not usually accompanied with any change in the cortex unless the cortex was bruised at the time of injury. This observation we have been able to verify in man in the case of old depressed fractures, the underlying cortex proving normal in every discernible aspect. While minor chromatolytic changes may occur in the nerve cells of the cortex compressed by extradural hemorrhage, subdural hemorrhage or hematoma, it is likely that a fatal issue ensues before destructive changes occur in these cells. In man, therefore, as in experimental animals, a loss of tigroid substance (whatever may be the nature and significance of this material) with minor nuclear changes is about all that one can expect to find as a consequence of pressure on the cortex.

NEURONAL CHANGES INCIDENT TO DESTRUCTIVE LESIONS OF THE CORTEX

The history of the study of changes in nerve cells as a result of local injury is now almost a century old, and yet there has been no known effort to survey these effects in any comprehensive way. Virchow [35] seems to have been the

33. Ugurgieri, C.: Compressioni sperimentali del sistema nervoso centrale: II. Compressioni cerebrali lente e progressive; reperti isto-patologici, Riv. di neurol. **7**:113 (April) 1934.

34. Naffziger, H. C., and Glaser, M. A.: Experimental Study of Effects of Depressed Fractures of the Skull, Surg., Gynec. & Obst. **51**:17 (July) 1930.

35. Virchow, R., 1857, cited by Dege.[42]

first to make such observations, noting the occurrence of "calcified" ganglion cells at the margin of old traumatic lesions of the cerebral cortex. Other observers also studied the cortical changes in wounds of the human brain (Tigges [36] Jolly,[37] Ceccherelli [38] and Popoff [39]) before the era of experimental investigation, which began in earnest about 1885. Oddly enough, these early experimental observations seemed to confirm the occurrence of nuclear division, a change which had been noted in cells at the margin of old cortical contusions, and one which had meanwhile been largely forgotten. Aside from the repeatedly observed karyokinetic figures in nerve cells at the margin of experimental cerebral wounds, little else was noted as a specific change until de Luzenberger [21] performed his interesting experiments by striking animals on the head with a hammer. As a result, he noted that the chromatin material (Nissl substance) in the nerve cells in the region of the blow had collected at one pole of the cell. Hauser [40] studied the changes in nerve cells in the margin of contrecoup lesions at the base of the brain and reported fragmentation and granulation of these elements. Bianchi [41] reported vacuolation, lipoidal degeneration and granulation of the neurofibrils at the margin of experimental injuries of the brain.

It remained for Cajal [15] to make a critical experimental study of the various changes in nerve cells as the result of local injury. With the use of his reduced silver method, he gave particular attention to the alterations in the neurofibrillar apparatus. He did observe, however, the occurrence of vacuolation, chromatolysis and pyknosis (sclerotic change). He found that the cellular fibrils underwent coarse or fine granulation (followed by cell death within a few hours), hirudiform alteration (with cell death in from three to seven days) and fusiform change, in which the individual neurofibrils formed fusiform swellings, which seemed to be a prelude to granular degeneration. He also noted that after two to four days the reticular apparatus of Golgi had undergone transformation. It was not possible to demonstrate the apparatus in the nerve cells adjacent to the wound, but slightly distant from the margin of the wound it was found to be reduced to granulations. Still more distant the apparatus was intact but in the form of large cordons and groups of loops and meshes.

In a general review of the problems of the pathology of cerebral injury, Dege [42] noted something of the historical development of knowledge of the histopathology of such injuries and commented briefly on the various changes observed in the nerve cells and fibers, as well as in the other elements. Among the various possibilities were mentioned "calcification," vacuolation, loss of granulation, atrophy, cell shrinkage and other regressive changes. He reviewed in some detail the observations of Ernest,[43] who was interested especially in the alterations in the Nissl substance after trauma, and those of Cajal, whose studies have already been mentioned. This review by Dege seems to be the most comprehensive survey up to this time, although it is not very long.

Since then a number of students of the problem of local cranial injury have made incidental observations on changes in nerve cells. For example, Penfield [44] noted that the cortical ganglion cells in the vicinity of experimental puncture wounds underwent a slow process of chromatolysis, which was quite evident after five weeks and which persisted as long as seven months. Staemmler [45] observed non-nucleated "ghost cells" about the margins of gunshot wounds of the cerebral cortex, as well as occasional instances of neuronophagia. Winkelman and Eckel [46] noted the occurrence of ischemic changes and tortuosity

36. Tigges, W.: Pathologisch-anatomische und physiologische Untersuchungen zur Dementia paralytica progressiva, Allg. Ztschr. f. Psychiat. **20**:313, 1863.

37. Jolly: Ueber traumatische Encephalitis, in Stricker, S.: Studien aus dem Institut für experimentelle Pathologie in Wien aus dem Jahre 1869, Vienna, W. Braumüller, 1870.

38. Ceccherelli, A.: Ein Beitrag zur Kenntnis der entzündlichen Veränderungen des Gehirns, Med. Jahrb., 1874, pp. 343-346.

39. Popoff, L.: Ueber Veränderungen im Gehirn bei Abdominaltyphus und traumatischer Entzündung, Virchows Arch. f. path. Anat. **63**:421, 1875.

40. Hauser, G.: Ueber einen Fall von Commotio cerebri, mit bemerkenswerthen Veränderungen im Gehirn, Deutsches Arch. f. klin. Med. **65**:433, 1900.

41. Bianchi, V.: Alterazioni istologiche della corteccia cerebrale in sequito a focolai distruttivi ed a lesioni sperimentali, Ann. di nevrol. **30**:61, 1912.

42. Dege, A.: Die traumatischen Schädigungen der Nervenzellen, Nervenfasern und des Nervenstützgewebes in Verletzungen des Gehirns, in von Bruns, P.: Neue deutsche Chirurgie, Stuttgart, F. Enke, 1920, vol. 18, pp. 70-75.

43. Ernest, P.: Das Nervensystem, in Aschoff, L.: Pathologische Anatomie, ed. 3, Jena, G. Fischer, 1913, vol. 2, pp. 343-428.

44. Penfield, W.: Meningo-Cerebral Adhesions: A Histological Study of the Results of Cerebral Incision and Cranioplasty, Surg., Gynec. & Obst. **39**:803 (Dec.) 1924.

45. Staemmler, M.: Ueber Veränderungen der kleinen Hirngefässe in apoplektischen und traumatischen Erweichungsherden und ihre Beziehungen zur traumatischen Spätapoplexie, Beitr. z. path. Anat. u. z. allg. Path. **78**:408, 1927.

46. Winkelman, N. W., and Eckel, J. L.: Brain Trauma: Histopathology During the Early Stages, Arch. Neurol. & Psychiat. **31**:956 (May) 1934.

of cell processes (pyknotic change) near foci of injury, which are now recognized to be the result of associated vascular change rather than an immediate effect of the injury. Hassin [11] called attention to this fact, suggesting that some of these changes are due to cerebral edema and ischemia. He described the alterations incident to acute traumatic degeneration, which, in the final analysis, is about the most characteristic traumatic change in these cells.

In describing the various changes in the cortical nerve cells as a consequence of local injury which we have encountered in the series of cases which form the basis of the present study, it has seemed advisable to describe all of the various alterations which have been encountered in the vicinity of contusions or lacerations of the cerebral cortex and then to try to evaluate their occurrence on the basis of the etiologic process which is most likely responsible for their presence. It will soon become evident that the accompanying vascular changes play an important part in the production of these alterations and that the problem is not made any simpler by the fact that more than one change may be present in a single cell. On this basis, the following alterations in these nerve cells will be described: (1) preservation necrosis (Cajal); (2) alterations in the reticular apparatus of Golgi; (3) pigmentary infiltration; (4) pyknotic (sclerotic) change; (5) ischemic change; (6) pigmentary atrophy; (7) vacuolar change; (8) acute traumatic change, minor and major; (9) multinucleation, and (10) ferrugination ("calcification").

Preservation Necrosis of Cajal.—As the result of his experience in studying the response of the brain to experimental trauma in the light of pictures produced by his reduced silver method, Cajal [15] was able to describe a peculiar type of reaction which he designated as preservation necrosis.

> . . . The least commotion, stretching or compression, especially when they are accompanied by diffusions of blood beyond the edges of the wound, bring about the almost instantaneous death of the nervous protoplasm and the peculiar phenomenon of *preservation*, that is, necrosis associated with the most perfect morphological integrity.

This interesting type of reaction we have been able to note just as clearly in cases of injury to the human brain as Cajal and his co-workers did in their experimental animals. If a block is taken from the cortex at the margin of a local contusion or in the vicinity of a small cortical hemorrhage and the individual sections are impregnated with silver by Cajal's reduced silver method, it will be found that the bodies of the nerve cells in the immediate proximity of the lesion, together with their axons and dendrites, are clearly demonstrated in all their details; these cells evidently have an unusual degree of affinity for the reduced silver. Such elements appear much blacker than do the uninjured cells somewhat farther removed from the margin of the lesion. This is an unusual situation, for, as Cajal has pointed out, these cells are dead elements, as is shown by their complete inability to react, as determined by following the changes manifested in a series of experimental animals. Cajal accounted for this phenomenon as follows: [15]

> This and other cases of maintenance of the morphology of the axon in consequence of hemorrhage show that, as we said in connection with the preserved fibers of the nerves and spinal cord, in the phenomenon of preservation a great part is played by some antiautolytic principle which proceeds from the sanguineous exudate and is fixed in the protoplasm of the axon.

As a result of this reaction, the various elements of the cell are even better demonstrated than those of the living neurons in adjacent regions of the cortex, even though the cells so demonstrated are completely defunct. In cases with longer survival period, the cells fail to show the typical response of living cells, with the formation of "buds, balls or other neurofibrillar reactions peculiar to traumatized axons." Not only are the dendrites and axons clearly demonstrated, but under suitable conditions the body of the nerve cells adjacent to these focal lesions will be found to show this preservation necrosis. The cells so affected will present a perfectly intact neurofibrillar apparatus and nucleus. The nonmedullated dendrites and regional nerve fibers are likewise perfectly demonstrated. Not all the cells at the margin of these wounds undergo this type of change, however; some of them give evidence of disintegration of the neurofibrils, nucleus and expansions. It is assumed that such cells have not been affected by the antiautolytic principle and are therefore already beginning to present evidence of their death. As Cajal has pointed out, unless one understands this fact, one may fall into considerable error in the interpretation of the histologic picture in the reduced silver preparations of tissue from the margins of lesions, even those of seven to ten days' standing. This phenomenon of preservation accounts for the delayed disintegration and phagocytosis of many of the parenchymatous elements at the margins of contusions and lacerations during this early period.

While this specific type of preservation necrosis is not peculiar to traumatic lesions (since it may be found in the region of cortical hemorrhages of any cause), it is characteristically ob-

served in such lesions as contusions or lacerations, which are invariably accompanied with some degree of effusion of blood.

Alterations in the Golgi Apparatus.—While our human material was not suited to a study of traumatic alterations of the Golgi apparatus, it seems worth while to make a brief note of Cajal's observations,[15] especially since we have found that the cellular alterations in man parallel so closely those observed in experimental animals. Cajal found that the reticular apparatus of Golgi was degenerated in the nerve cells in the margins of cerebral wounds of kittens or puppies killed from two to four days after the wound had been made. The amount of the damage was dependent on the degree of commotion or contusion of the brain tissue produced at the time of the injury. At the very edge of the wound, the reticular apparatus was completely degenerated. Somewhat more removed from its margin, the reticulum was fragmented, granular and at times reduced to dust. Still more remote from the wound, this structure had been converted into a series of loops and meshes, which was often found entirely on one side of the displaced nucleus. Distal to this zone the reticular apparatus appeared entirely normal.

These observations suggest that the cells adjacent to the margin of the wound were dead, for in dead cells the reticular apparatus disintegrates rapidly. In the less damaged, and more distal, cells the minor alterations in this structure were probably reversible, representing only the early stage of the process of change.

Pigmentary Infiltration.—It has long been recognized that the nerve cells in the vicinity of hemorrhages often contain a brownish granular pigment. This was once designated as "formalin pigment" and was thought to be due to the demonstration of some preexistent substance in the cell incident to fixation with solution of formaldehyde U. S. P. No doubt such pigmentation of nerve cells has likewise been previously observed in the case of traumatic hemorrhage, although little seems to have been made of it. Winkelman and Eckel [16] reported finding such pigment in the nerve cells in the vicinity of traumatic cortical hemorrhages, and we have frequently observed it in similar circumstances. While it is not necessarily an exclusive traumatic change, it is of frequent occurrence in cases of contusion (in which hemorrhage is conspicuous), as well as in cases of cortical and subcortical traumatic hemorrhage. Therefore a brief description of the change and something said about its possible significance will not be out of order.

In the series of specimens which formed the basis of this study, pigmentary infiltration of nerve cells was found within a few hours after cranial injury and as long as three and a half days after such injury, always in the immediate vicinity of an effusion of blood into the cortex. The amount of pigment was greatest in the cells in the immediate vicinity and decreased with the distance from the hemorrhage. In the cells near the effusion the pigment granules were larger, were round or oval and were frequently found in all portions of the cytoplasm, but not in the nucleus. In these circumstances, the cellular details were sometimes entirely obscured by the mass of pigment. In the cells somewhat removed from the contusion the injured pigment occurred in the form of fine grains and was found most often in the periphery of the cell or limited to one pole (fig. 5). Since more pigment was found in the cases with longer survival periods, it is suggested that the process must be a progressive one, at least up to a certain point.

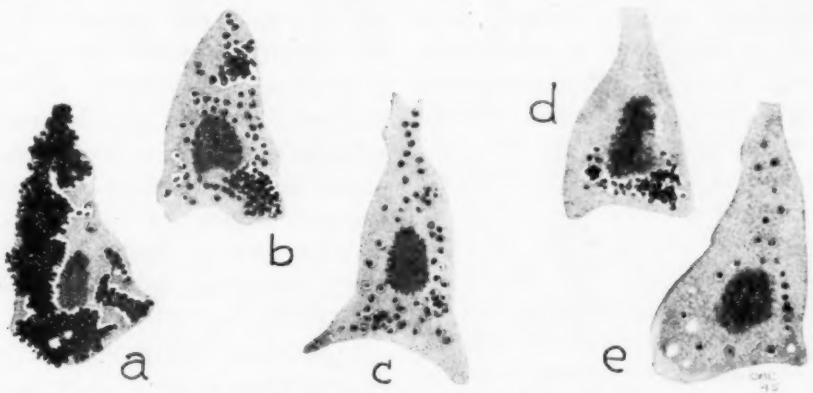

Fig. 5.—Pigmentary infiltration in the vicinity of cortical hemorrhage (contusion), showing varying amounts of hematogenous pigment in (*a*) nerve cells immediately adjacent to the hemorrhage and (*b* to *e*) cells progressively removed from it (*c*, diffuse spread, and, *d*, localized collection of pigment in the cytoplasm). Survival period, six and three-fourth hours.

Examination of the pigment granules with the aid of the higher powers of the microscope indicates that these granules very likely result from the agglutination of many small, powder-like grains of pigment material. The larger grains often assumed an irregular and finely nodular shape, which further suggested such an origin. These large nodules, somewhat darker than the fine grains found in the cells more removed from the margin of the hemorrhage, were also observed to have a lighter-colored center, similar in shade to that of the finer grains. It may be that some action of the cellular cytoplasm agglutinates the pigment granules and imparts a darker color to them.

Pigment of similar nature was also occasionally found in other cellular elements in the vicinity of the hemorrhage, suggesting that the pigment was hematogenous and came from disintegration of the red cells. At times it was observed in some of the interstitial cells, chiefly the microglia elements, especially when they had assumed the characteristics of compound granular corpuscles. In these cells the pigment granules were large, often irregular and almost black. At times it appeared as though this pigment was also contained in astrocytes, although always in small quantities. It was found in abundance in the endothelial cells of the regional capillaries.

We are of the opinion that this pigment is hematogenous and is derived from red cells of the hemorrhagic effusion. The reasons for this conclusion may be enumerated as follows: (1) In the immediate vicinity of the hemorrhage fine grains of similar pigment may be found loose in the tissues, suggesting that it is derived from the hemorrhagic effusion; (2) the pigment is most abundant in the nerve cells in the immediate vicinity of the hemorrhage, becoming less and less evident with the distance of the cells from the margin; (3) the presence of the pigment in other elements, especially the regional macrophages and the endothelial cells of the small vessels, indicates that it is a substance of local origin, not due simply to formaldehyde fixation of the tissues, and (4) pigment-laden nerve cells are found only in the vicinity of such hemorrhages. The very fine particles of hemoglobin which are released when the red blood cells disintegrate are apparently carried in suspension in the tissue fluids. The small size of these grains permits them to be carried into the nerve cells in the course of interchange of cellular fluids, perhaps aided by the excess amount of fluid incident to edema. Once in the cell, the cytoplasm acts to agglutinate the particles into larger granules, which soon become evident in the nerve cell, even under the lower powers of the microscope. The suspension of such grains in the tissue fluids, thus accounting for their being carried into the cell, is also suggested by the fact that isolated granules in the cytoplasm of the cell are often observed to be surrounded by a small vacuole.

The effect of such pigment on the nerve cell is conjectural. We have found no evidence that it has any specific lethal effect on the host when present in small amounts. While we have not chanced to observe it later than three and a half days after the injury, it may be present for a longer interval. At the end of fourteen days, for instance, we have observed golden yellow inclusion particles in regional nerve cells, their presence suggesting that the pigment continues its process of disintegration within the nerve cell as it does outside, passing through the usual stages of coloration in the process. While the pigment has been observed in "ghost cells" in the vicinity of local traumatic cortical lesions (sometimes the outline of the cell is clearly delineated by the distribution of the pigment granules), there is no evidence that the pigment produced the death of the cell unless it was excessive in amount. The release of pigment by disintegration of heavily charged cells, on the other hand, may indicate that large amounts of it may lead to death of the cell.

Pigmentary infiltration, as we have chosen to designate the process, is not infrequently found in association with other types of cellular alteration—sclerosis (pyknosis), acute degenerative changes, edema and ischemic change. As will subsequently be emphasized, this multiplicity of changes in a single cell not infrequently occurs, making evaluation of the nature and causes of the end picture a somewhat complicated procedure.

Pyknotic Change.—This type of alteration of the nerve cell, which has long been known, and under a variety of names, such as "chronic cell disease" (Nissl), "shrinkage of nerve cells" (Bielschowsky) and sclerotic change, has been found in a number of conditions but is most commonly observed at the margin of areas of softening and recent hemorrhages incident to vascular disease. It is therefore only secondarily a traumatic change of the nerve cell, being found most commonly at the margin of traumatic cortical hemorrhages, which constitute a considerable proportion of local contusions. Cajal [15] reported this change near the margins of experimental cortical wounds, and Winkelman and Eckel [43]

observed similar cells at the margin of cortical lesions in which vascular change was present.

In our cases pyknotic change was almost invariably present, at least to some degree, at the margins of traumatic cortical hemorrhages. While a similar change of mild degree was sometimes seen (as has also been observed by Hassin [11]) in cases in which there was extensive cerebral edema, it may be said that in its major and classic form the reaction is essentially a local one. It occurs early (within the first few hours after injury) and apparently persists for some time (at least three and one half days in this series). It is possible that such pyknotic cells may be overcome in the advancing marginal zone of degeneration, but undoubtedly individual cells persist for some time, as the shrunken type of iron-encrusted cells of long duration definitely suggests. We have found this change to occur typically just distal to the zone of preserved cells, exactly as Cajal observed them in his experimental cerebral wounds.

In its typical form, the pyknotic cell is shrunken, especially in its long axis; the cytoplasm usually stains a deep reddish or bluish purple, and little structure is to be made out. The compressed, elongated and often pyramidal nucleus likewise shows little structural detail, being manifested only by a none too sharply defined clear area in the central part of the cell. The margins of the cell, usually fairly regular and smooth, are concave. The evident dendrites are few, they stand out sharply, owing to their dark coloration, and the tortuous (corkscrew) apical process can be traced for some distance above the body of the cell. These cells are often found in obviously distended pericellular spaces, which betray the presence of excess tissue fluid. There is at times an associated shrinkage of the surrounding interstitial tissues.

Fusiform Alteration.—One occasionally sees small nerve cells which present a fusiform shape in the region next to focal cortical hemorrhages of traumatic origin. Because these cells are invariably found in this location, because they are always observed where typical pyknotic cells occur and because they present definite characteristics which suggest this change, it has been assumed that they are but one type of pyknotic cells. Since they are small, it is assumed that they are somewhat altered and represent the fusiform (polymorphic) elements which are present in the deep layer of polymorphic cells of the cerebral cortex. This conclusion seems to be correct, since these cells are seen in cases with very short survival periods (one hour). Be this as it may, it is sufficient to say that these elements are found in the shape of an elongated oval, presenting an apical and a basilar process, occasionally with a lateral expansion. The elongated nucleus is frequently characterized by the presence of a variably sized nucleolus. The processes of these cells, especially the apical one, are tortuous. With the Cajal reduced silver method, the neurofibrillar substance is usually seen to be varicose, or broken up into coarse or fine granulations, or to form a reticular network in the basilar portion of the cell (fig. 6).

Fig. 6.—Pyknotic change ("sclerosis") in the bipolar cells in the deeper layers of the cortex adjacent to contusion. Granulation of neurofibrillar elements as shown with Cajal's reduced silver method. Survival period, about two hours.

Because of the location of these pyknotic or sclerotic cells, near the margin of contusion hemorrhages of the cortex, it is not surprising that this type of change is modified with the presence of change of other kinds. Not infrequently one finds pigmentary infiltration in cells otherwise typically sclerotic. The process of preservation apparently also overtakes cells which have already begun to show this type of alteration (seen in cases with a survival period as short as seven hours and as long as seven and a half days). The occurrence of vacuolar spaces in the basilar portion of some of the cells suggests that pyknotic changes may be succeeded in certain

circumstances by some degree of severe cell change (traumatic degeneration). Some cells which show typical morphologic alterations but in which the cytoplasm stains a pinkish or copper color suggest the further possibility that ischemic change might alter its appearance Some of the various possibilities are indicated in figure 1.

As has already been pointed out, this type of nerve cell change is not typical of injury but is one which is found in many circumstances and under many conditions. Since it is most common at the margin of areas of softening or local cortical hemorrhages, it is assumed that its occurrence is best explained by some local disturbance in circulation. This seems to be demonstrated by the fact that in this series of cases it was typically found at the margins of traumatic cortical hemorrhages and in regions next to focal lesions where edematous change was pronounced. Pyknotic change, therefore, is only indirectly a post-traumatic alteration in nerve cells, being secondary to such vascular disturbances in the cortex as may by chance be produced by the traumatic lesion, which usually occurs in the form of local hemorrhages.

Ischemic Change.—This alteration is rare with traumatic lesions of the cortex and, when present, is invariably due to some associated vascular lesion. Neubürger [16] described it as a distant change (hippocampus) following gunshot wounds of the head and attributed it to some general effect of the wound on the intracranial vascular system. Winkelman and Eckel [46] described it as occurring near traumatic foci in the cerebral cortex.

Ischemic changes as a consequence of traumatic cortical lesions seem to occur in two forms: (1) as an atypical, copper-colored cell, found at the margins of very recent lesions, and (2) as a typical ischemic cell, which is commonly observed in the cortex adjacent to a contusion after an interval of seven days or more. The cell showing atypical ischemic change is characterized by loss of chromatic substance from the cytoplasm, some degree of shrinkage of the cell and the assumption of a peculiar and characteristic copper color. The steps leading to the formation of such a cell, beginning at a short distance from a contusion and extending up to its margin, are shown in color in figure 1 (a^1 to a^5).

The typical ischemic change has been found, in our experience, only after a week or more has elapsed since the time of the injury. In a study of a series of sections from the margins of contusions of persons who had survived their injury for an interval of seven to ten days, the cytoplasm of the regional cortical nerve cells was found to present a typical ground-glass, agranular appearance. The cytoplasm stained a brilliant orange-pink with eosin. The cell body was slightly shrunken and seemed to merge, without much distinction, into the surrounding interstitial tissue, suggesting that a slow process of cell disintegration had already begun. The appearance of these cells is indicated in figure 1 (*d*). This change, which may be preliminary to multinucleation, to be described later, is evidently the result of circulatory disturbances at the margin of cortical bruises and lacerations. On this basis, it may also be assumed that similar alterations would be found at the borders of cortical softening incident to traumatic thrombosis of the cerebral arteries.

It is therefore to be concluded that typical ischemic change is rarely found as an alteration in the cortical nerve cells in case of trauma and then only in response to some traumatic vascular lesion and after an interval of one to two weeks. An atypical form of this change, based on the peculiar staining reaction of the cytoplasm of the affected nerve cells, may be seen in which the cytoplasmic change occurs in cells showing other types of degenerative change.

Lipoidal Change in Nerve Cells.—Pigmentary atrophy, as the localized collection of pigment in the paranuclear zone of the nerve cells of older persons has come to be called, like pyknotic and ischemic change, must be considered at best only an indirect effect of trauma. In any circumstances, its production as a result of trauma is unusual. Mühlmann [47] found such changes in the nerve cells of the nucleus of the vagus nerve after injury and assumed them to be of traumatic origin. Bianchi [41] found lipoidal change in the nerve cells adjacent to experimental focal injury.

While we found evidence of lipoidal change in a number of the cases studied, it seemed clear

47. Mühlmann, M.: Weitere Untersuchungen über die Veränderungen der Nervenzellen in verschiedenem Alter, Arch. f. mikr. Anat. **58**:231, 1901; Verhandl. d. deutsch. path. Gesellsch. (1900), 1901, pp. 148; Anat. Anz. **19**:377, 1901.

that in most instances it was due simply to the advanced age of the patient and was not to be attributed to injury to the head. At the margins of the cortical contusions in some of the older lesions (two weeks or more) some of the nerve cells were found to contain a deposit of lipoidal pigment which stained a bright red with sudan IV (fig. 1). This seemed to be an unusual change and was probably a true traumatic effect, since it was found in persons in the third decade of life. This conclusion seems to be verified by the fact that it was a local, and not a universal, alteration.

It is generally agreed that pigmentary atrophy is to be considered a slowly regressive change, indicative of progressive senility. This change is probably the result of minor impairment of nutrition, or perhaps, more accurately, of cellular respiration. This is suggested by the fact that similar changes have been observed as a relatively acute process in cases of asphyxia in which the patient survived the episode for a few weeks (Courville [48]). On this basis, it may be assumed that any cortical lesion in which there is impairment of tissue respiration may be the seat of lipoidal change in the regional nerve cells. Such seems to be the case in some of these focal traumatic cortical lesions which are old enough to permit such changes to occur and about which the necessary disturbance in circulation has occurred. On this basis, then, pigmentary atrophy is to be considered a local circulatory change occurring as an alteration incidental to, and not as a direct consequence of, injury.

Local Edematous Change in Nerve Cells.—Attention has already been drawn to certain minor changes in nerve cells which apparently occur as a generalized alteration as a consequence of traumatic edema of the brain. These changes consist in vacuolation of the nucleus and nucleolus, with semilunar perinuclear "halos," which are apparently small circumscribed collections of fluid. Rarely, vacuoles of small size may be found in the cytoplasm itself. The reason that these changes are so inconspicuous is that rarely does traumatic cerebral edema become so profound as even to simulate the typical picture of edematous cell change observed in animals which have been experimentally hydrated by the intravenous injection of hypotonic solutions.

On the other hand, it is quite generally recognized that local edema about regional cerebral wounds is much more pronounced than general edema. It is therefore not unreasonable to expect that the local effects of edema on nerve cells will be much more permanent than the general effects. One reason that such changes are not better defined is that they are overshadowed by other, and more serious, alterations in the cellular elements. Nevertheless, in the vicinity of these wounds, routine stains often disclose more or less conspicuous vacuolation of the nerve cells.

Scagliosi [8] found vacuoles in nerve cells twenty-four hours after experimental injuries to the brain. The Nissl method was used to demonstrate these vacuoles. These vacuolar changes were also observed by Bianchi [41] in nerve cells in the vicinity of experimental cortical wounds. Cajal [15] also saw vacuolated neurons in association with experimental injuries of the cortex. When the change is extensive, the large, smooth-contoured, round or oval vacuoles come to obscure to a considerable degree the normal structure of the cell.[49]

Segmentation of the Nerve Cell.—In his now memorable study on the nerve cells, Ewing [32] described clefts and fissures of nerve cells as a type of cell change. Similar changes have been observed by us. In these cells, which are extensively vacuolated (fig. 7), indentations or fissures extend from the margin of the cell into the cytoplasm or nucleus for variable distances. In some instances, the fissure passes entirely through the cell, one or more such fissures at times breaking it up into several segments. Whether this segmentation is the result of a collection of extracellular fluid which pushes its way into the cell or whether the interruption of cell membrane is a result of rupture of a fluid-filled vacuole is, of course, conjectural. At first these observations were thought to be artefacts, due to improper fixation or staining, but on closer study it seems fairly clear that this process of segmentation is simply

48. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129 (May) 1936; Untoward Effects of Nitrous Oxide Anesthesia, Mountain View, Calif., Pacific Press, 1939.

49. It is advisable to point out that the simple presence of vacuolar spaces in the cytoplasm of the nerve cell does not necessarily warrant the diagnosis of vacuolar change. As will be shown in a subsequent section, serious degrees of traumatic degeneration of the nerve cell are accompanied with the formations of vacuoles, which often completely fill the cytoplasm of the cell. Even when these vacuoles are of fluid nature (which they sometimes are not, being due to inclusion forms not stained by the method being used), one is not privileged to say that their presence is due to edema.

an advanced stage of local edematous change which leads to destruction of the nerve cell. As evidence for this conclusion are the numerous vacuoles which are already found to be present in the cytoplasm and nucleus,

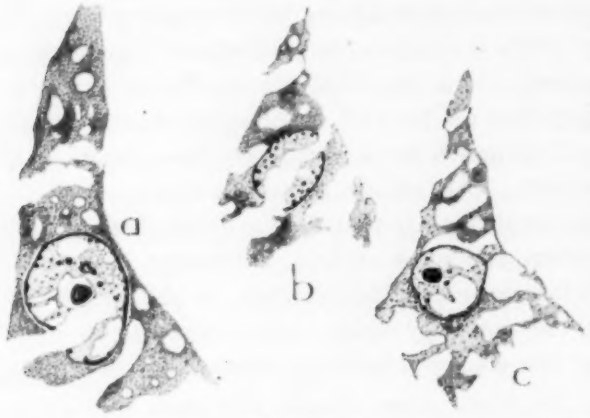

Fig. 7.—Vacuolation and segmentation of nerve cells adjacent to local cortical injury, apparently the result of local edema. Bielschowsky-Plein stain for tigroid substance; Survival period six and three-fourth hours.

the apparent rupture of many of these vacuoles through the cell, and even the nuclear membrane, and the ragged appearance of the borders of the cell.

Edematous change, therefore, may be a generalized and relatively mild type of alteration of the nerve cell, or it may be extreme, and may even lead to cell destruction when it occurs in the vicinity of a local traumatic lesion of the cortex. This change may also be present to variable degrees in cells in which other types of alteration are in evidence.

Acute Traumatic Change.—By this time it has become apparent that the alterations which occur in nerve cells in response to injury are not in any case greatly different from, and in many instances quite the same as, those which may occur from any other type of pathologic process. Perhaps the most disturbing feature in efforts to evaluate the nature of cell change is the occurrence of multiple processes acting on a single cell. This principle still holds good for the most typical of the cellular responses to trauma, which may be included under the general heading of "acute traumatic change." Of this type, there may be distingushed three morphologic subtypes, each of which seems to conform to a fairly characteristic pattern. But even in these subtypes one is able to trace definite similarities to the various specific types of cell change which are already well known. Each of these variants will be briefly described before a more detailed description of the alterations in the various structures of the nerve cell is given.

Acute Traumatic Chromatolysis: This type of change in ganglion cells is observed near the margins of minor and experimental injuries (Penfield [44]) or traumatic lesions or at a greater distance from the borders of major ones. It differs perhaps only in rapidity of development and in degree from those alterations which we have already observed as a general effect of the shock of cranial injury. As Hassin [11] has pointed out, it is practically identical with the change which Nissl described half a century ago as "acute disease of nerve cells." This alteration is characterized in cases of traumatic lesions by a minor degree of swelling of the cell, progressive loss of tigroid granules, which begins in the perinuclear region, and eccentration of the nucleus and nucleolus, with alteration in shape of the nucleus due to shrinkage, which results in the formation of folds in the nuclear membrane. The cell may subsequently show evidences of the more severe types of alteration if it chances to be located in the path of a progressive advance of the zone of degeneration and, as has been pointed out, may show the presence of other types of alteration incident to the traumatic lesion.

Acute Total Disintegration: At the margins of acute traumatic lesions of the brain are invariably found a number of cells which are evidenced in the preparations of the various methods only by a shadowy outline. These cells, for this reason, have been designated as "ghost cells." These cells were noted by Cajal [15] at the margin of his experimental wounds of the cortex. They may be found in cases of injury of the human cortex as early as an hour or two of the injury and as late as thirty-nine days after cranial trauma. This late occurrence of such cells suggests either that they are capable of surviving longer than their pallid appearance would suggest or that perhaps the change occurs progressively in the margin of these wounds. It may also be that the failure of these cells to take stains or to become impregnated with metals may not be a true indicator of their viability, for such cells containing hematogenous pigment have been found at the margins of traumatic cortical hemorrhages. Whatever may be their state of viability, these cells constitute a type of reaction to injury, in which the cell seems to fade out of the picture *en masse.* This may be due to the fact that the injury occurred at a moment when these individual cells were at a low point in their metabolic or physiologic activity, and the force of the trauma rendered them *hors de combat,* a shock which their more resistant neighbors were able to withstand, at least for the time being.

Acute Progressive Necrosis: This type of change in the nerve cells, which is found at the margin of traumatic cortical lesions, corresponds fairly closely to the "profound nerve cell change" (*schwere Zellveränderung*) of Nissl, though it is modified somewhat by associated pathologic conditions also acting on it and the speed with which complete disintegration takes place. This change is characterized by early evidence of cell death in the form of irregularity of the cell margin, vacuolation of its cytoplasm and rupture of the nuclear membrane,

followed by fragmentation of the processes and disintegration of the cell body. This process is evidently one of decadence affecting a cell which was killed by the shock of the injury and/or the traumatizing action of foreign bodies or hemorrhage on the cortex. It is therefore found at the margin of the area of destruction and within the zone of progressive degeneration which borders this area. Such a degenerative change is usually completed in twelve to fourteen days, at the end of which little evidence is to be found of the structures which originally occupied this bordering zone. The change, however, may progressively involve adjacent regions if further disintegration occurs as a result of acute or chronic vascular disorders which are initiated by the traumatic process. This is particularly true of cortical lacerations with very irregular margins, in response to which a meningocerebral cicatrix is formed.

After this consideration of those special entities which had not already been included with the types of traumatic alteration of nerve cells, attention may now be given to the more detailed changes in the various cellular structures which are the apparent direct result of injury to the regional cortex.

Alterations in the Cell Membrane.—These changes are found almost exclusively in the cells which undergo acute necrotic changes. With the majority of the other types of alteration, the membrane seems to preserve its integrity fairly well. In the "ghost cells" the cell membrane, as well as the other characteristic structures of the cell, is not amenable to demonstration with the usual methods of staining and impregnation. Satellite cells may pass through the cell membrane in the occasional examples of pseudoneuronophagia which may be found at a little distance from the margin of the wound. The membrane may also be interrupted by ingress or egress of large fluid vacuoles, found in cells undergoing "segmentation" as already described. Otherwise the change in the cell membrane is largely a matter of disruption of this structure as a natural consequence of progressive disintegration of dead elements at the margin of the lesion. This is found as an almost immediate consequence of trauma (within a few hours), associated with the breaking off and fragmentation of the cell processes and, later, complete disintegration of the cell (fig. 8). It is possible for only a part of the cell to show these changes at first, suggesting a focal injury of such an element. It is likely that such a focal injury is incompatible with the life of the cell and that ultimate destruction results.

Changes in the Cellular Cytoplasm.—These changes are numerous and variable. In this connection, we are concerned only with alterations in the fundamental protoplasm of the cell, not with the contained formed structures, such as the tigroid substance, the neurofibrils or the Golgi apparatus. These changes may be described as (1) homogenization, (2) pigmentary and lipoidal deposition, (3) formation of granules and (4) vacuolation.

1. Homogenization in the region of focal injury seems to be a modified form of ischemic cell change, described by Spielmeyer. The cytoplasm loses its tigroid material and thus becomes agranular. This is followed by a uniform ground-glass appearance of the cytoplasm, which assumes first a bright pink and then an orange-pink copper color. These progressive changes can be observed in a single case by first studying the elements removed from the influence of the trauma and then noting the changes as one approaches the margin of the contusion. This is best seen, according to our experience, in cases with a survival period over twenty-four hours, a fact which suggests that time is a factor in the development of these characteristic changes. Cells of this type immediately adjacent to the margin of the lesion often show vacuolation at the base of the cell, suggesting that degenerative changes of a more acute variety had supervened.

2. Pigmentary deposits were of two types. Pigmentary infiltration, with the collection in the cytoplasm of hematogenous pigments in the margin of traumatic cortical hemorrhages, was the rule in cases of such an injury, a process which has already been described in some detail. Such pigment may apparently undergo regressive chemical changes within the cell, for after a week or more bright yellow granules may be found in cells at the margins of recent hemorrhages. Pigment atrophy (lipoidal change), characteristic of advancing years, may be found in the ganglion cells of older persons, in which it is an incidental change, and not a consequence of injury. However, a similar development may occur in younger persons at the margins of cortical contusions and lacerations at the end of two weeks. It is suggested that this is due to vascular change which results in a degree of cellular anoxia, since similar changes do occur as an effect of asphyxia (fig. 1).

3. The occurrence of abnormal granular products is almost exclusively an evidence of acute degeneration of nerve cells and is found in such elements after several days in phosphotungstic acid hematoxylin and aniline blue preparations. These granulations are found to be fuchsinophilic or basophilic in reaction and are usually round or slightly oval and small. They are found in the cytoplasm of the nerve cells which show other evidence of cellular disintegration.

portion of the cell. Such granulations are also represented by the formation of vacuolar spaces in the cytoplasm in routine preparations. Vacuolation of the nucleus, the nucleolus and, at times, the cytoplasm of the cell is found most often as a consequence of edema. In the presence of severe wounds, this process may be present to a degree in which vacuolation of the cytoplasm also occurs. This begins at first with the formation of semilunar clear spaces about a portion of

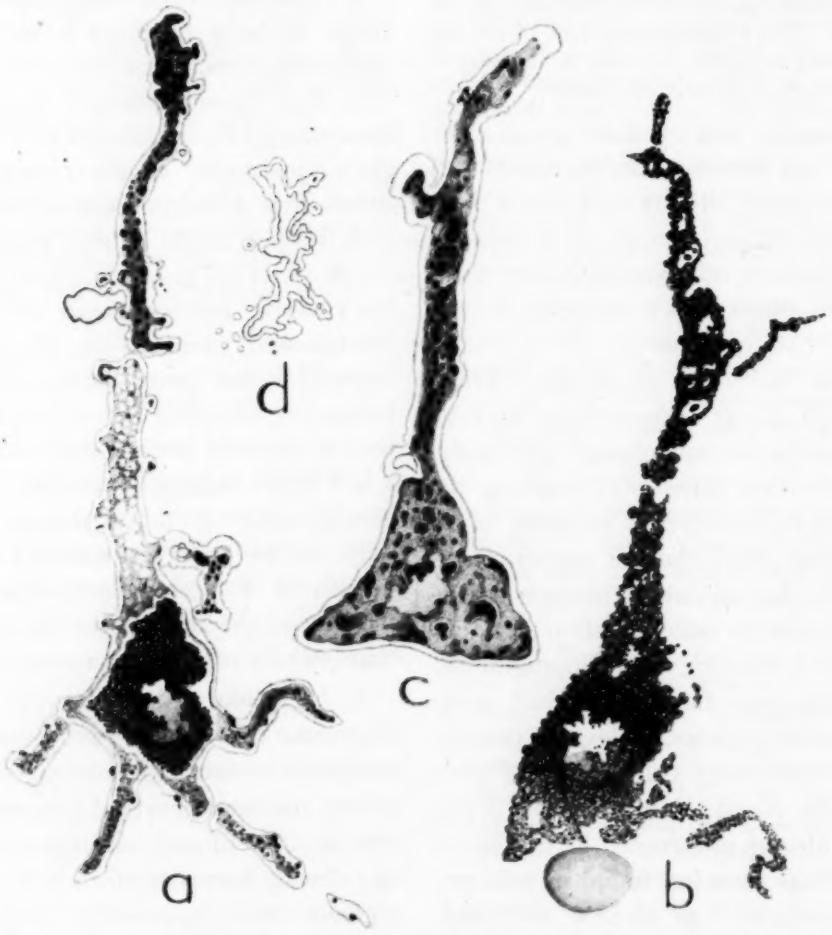

Fig. 8.—Disintegration of nerve cells ("traumatic degeneration") in the vicinity of a cortical contusion, showing fine (*a* and *b*) and coarse (*c*) granulation of the neurofibrillar elements. Cajal's reduced silver preparation; survival period, thirty-five days.

4. The formation of vacuoles in the cytoplasm of the nerve cells at the margin of an injury has a varied significance. In cells undergoing acute necrosis, such vacuoles may represent spaces or defects in the cell, for no staining method brings out any positive physical structure. These spaces are small at first but increase in size progressively as the cytoplasm breaks down. Special stains will show, at the same time, the presence in the cytoplasm of fuchsinophilic and basophilic granules of smaller size, and usually in the basilar

the nucleus. Then vacuoles are formed in the cytoplasm in the basilar portion of the cell. With extremely severe wounds vacuoles of this type completely fill the cell, contributing in some instances to "segmentation" of the cell, as described elsewhere.

Changes in the Tigroid Substance.—Changes in this substance occur as one of two types: (1) dissolution, or chromatolysis, and (2) fusion, or agglutination, of this material. Chromatolysis is evidently the simplest type of reac-

tion of this substance and occurs in the nerve cells at the margins of simple puncture wounds or minor contusions. This process usually begins in the perinuclear region, where a clear zone is formed. As the process spreads concentrically, the larger granules are broken down into their finer constituents, leaving a ring of fine, dustlike particles. Tigroid material then disappears from the basilar region of the cell and finally from the apical region, where it tends to persist the longest. Ultimately, even the fine bluish granulation disappears, leaving an agranular cytoplasm.

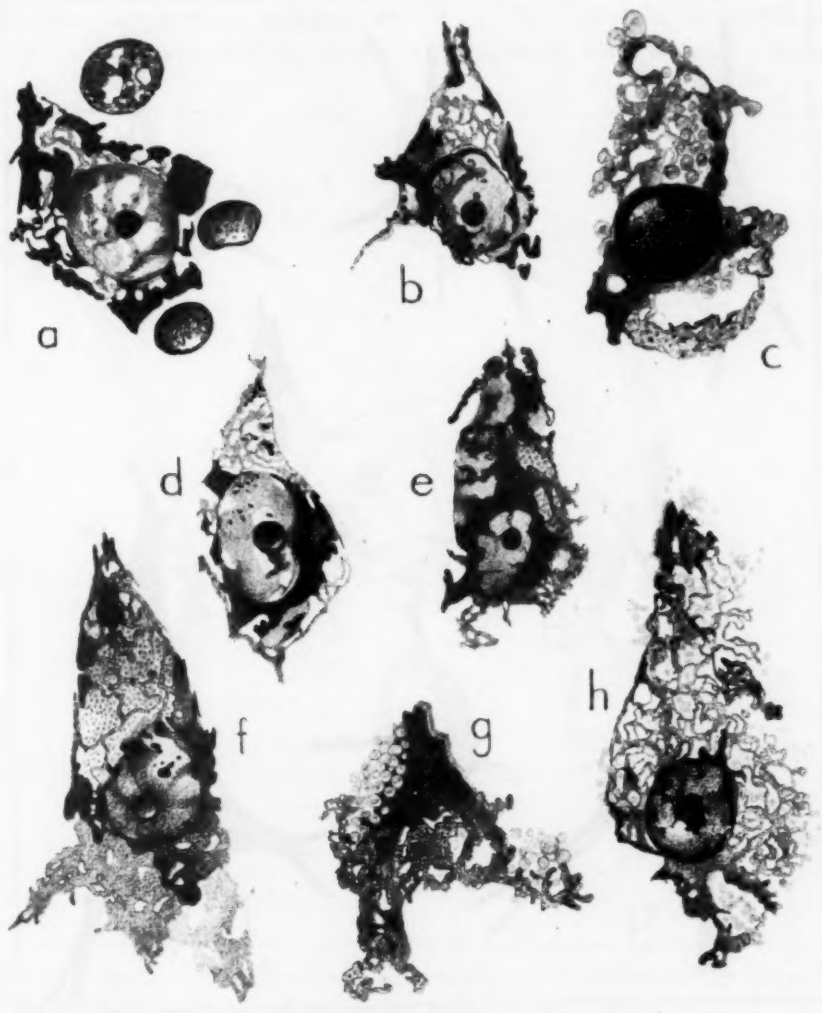

Fig. 9.—Condensation of chromatin material (tigroid substance) in nerve cells in the vicinity of a cortical contusion, showing associated vacuolation and fenestration of cells; (*f*) deposition of lipid pigment. Bielschowsky-Plein method for Nissl substance; survival period, three days and nineteen hours.

Fusion of the tigroid granules seems to be a process associated with acute traumatic degeneration of nerve cells, being found after two or three days in those elements destined to disintegrate. This is evidenced by the marked irregularity of the cell outline, the occurrence of vacuolation of the cytoplasm and the breaking up and disappearance of the nucleus. In these cells the chromatic granules tend to lose their characteristic shape, size and structure, assuming the appearance of irregular masses of a deep blue appearance and a homogeneous, waxlike structure (fig. 1). At times, these large, irregular masses occupy a goodly portion of the remaining cytoplasm; at others, only one or two isolated masses are left. Occasionally, the peripheral nuclear granules fuse to form a dark, irregular ring about what remains of the nucleus. It is assumed that the necrotic process has resulted in some chemical change in the tigroid substance, causing it to "melt" and fuse into these irregular masses. These changes are shown in figure 9.

Alterations in the Neurofibrillar Structure.—These changes are interesting and complex. It must be recognized that the changes observed

in the reduced silver preparations differ much from those in sections prepared with the Bielschowsky method. In order to compare Cajal's observations in experimental wounds, it seems best to describe their human counterpart on the basis of this staining differential.

Cajal described several types of alterations in the neurofibrils of his experimental animals. The first changes seemed to be hypertrophy and varicosity of individual elements, followed by breaking up of these segments into fusiform fragments. This process was followed by the formation of coarse, and then of fine, granules. Rarely, a reticular formation seemed to result from the central neurofibrils. At times, this disintegration first involved the periphery of the cell, leaving an external clear zone (hirudiform change); in other instances, the central portion of the cell was first affected. It is reasonable to believe that this is the typical process in the disintegration of these elements. Since injury was due to simple incision of the cortex, blunt force did not enter into the problem.

A somewhat different situation exists in the case of injuries to the human brain. With contusions and lacerations of the brain, the element of shocking force is introduced, which was not present in the simple cortical incisions of Cajal. It has therefore been found that there is an almost immediate granulation of the neurofibrils in the cells at the margins of acute cerebral wounds. In other words, the injury to these cells is so profound as to produce the end stage of disintegration at once. However, in the cells more distant from the margin of the traumatic lesion, one is able to find varicosity and fusiform degeneration after a few days, followed, in turn, by coarse and fine granulations. Since reticular formation has also been observed, we have been able to find in the injured human nerve cells all the counterparts of the changes described by Cajal.

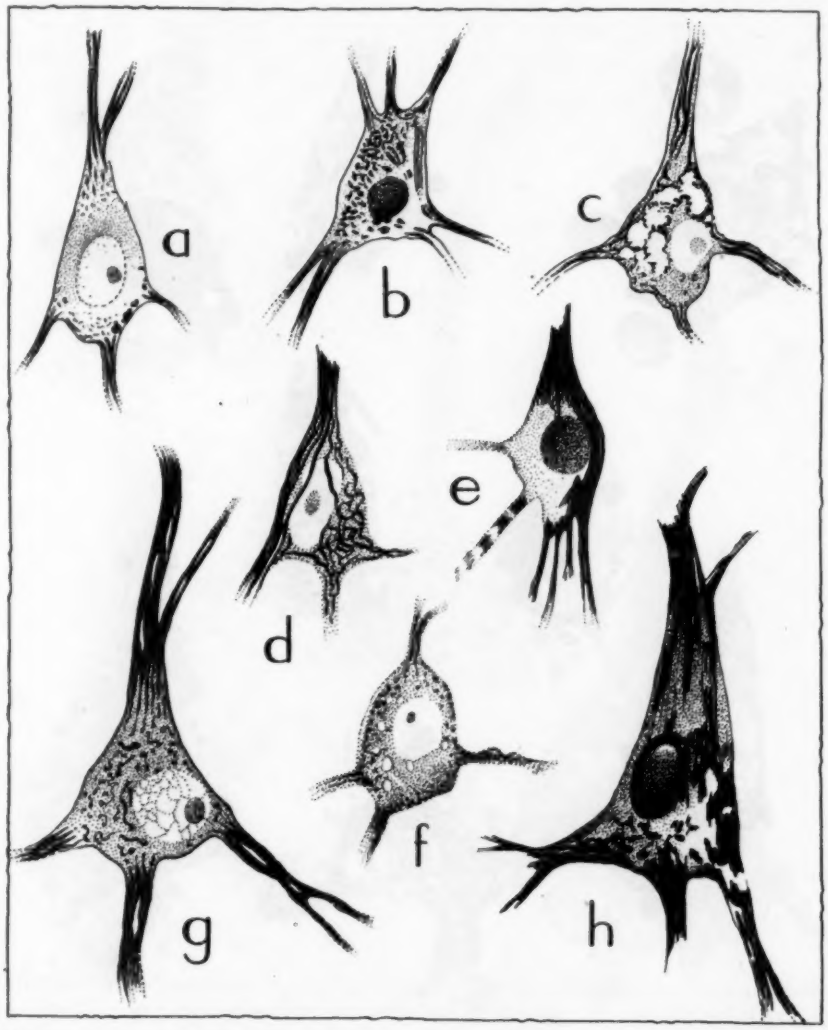

Fig. 10.—Alterations in the neurofibrillar pattern in nerve cells as a result of trauma, showing (*a*) fine granulation, (*b*) coarse granulation, (*c*) tortuosity and net formation, (*d*) varicosity and reticulation, (*e* and *h*) patchy degeneration, (*f*) fine and coarse granulation and (*g*) fragmentation. Cajal's reduced silver stain; survival period, thirty-one hours.

The appearance of individual cells differed greatly. As is shown in figure 10, the central portion of a cell may be completely devoid of any normal fibrils, or even of the larger residual fragments of them. In other cells small fragments, either lying loose in the cytoplasm or gathered about vacuolar spaces, could be seen. In these cells fairly well preserved elements were to be seen in the processes. In some cells both fine and coarse granulations, resulting from disintegration of these elements, were observed. Some cells presented a peculiar patchy, or barred, appearance, which was due to spotty degeneration of entire groups of fibrils, for which no specific reason can now be assigned.

A study of individual fibrils brings to light some interesting observations as to the process of disintegration of these structures. Although as a rule all of the fibers in the body of the cell are affected alike, this is not invariably the case. One may see fairly normal fibers passing through the cell body occupied largely by the granular remains of these elements. Or one may observe a number of fusiform granules along with fine or coarse granulation. Individual intact fibers may be hypertrophied and varicose to a conspicuous degree. Occasionally, bizarre patterns may be formed by the fragments of these elements. Some of these alterations in individual elements are shown in figure 11.

All these alterations, whether they are gross or detailed, seem to be more advanced in the smaller pyramidal cells than in the medium-sized or the large ones. These smaller cells are evidently more susceptible to the effects of injury.

In the Bielschowsky preparations, a rather less intense, and somewhat delayed, disintegration of these elements is present. The neurofibrillar elements do not show early alterations and seem to pass through a different series of steps in the process. In some cells the formation of a peculiar reticular network seems to be an interim stage. In other cells what seems to be the formation of tiny vacuoles within or between individual fibers (observed under the oil immersion lens) seems to take place before degeneration occurs. Hypertrophy and varicosity are much less evident, although they, too,

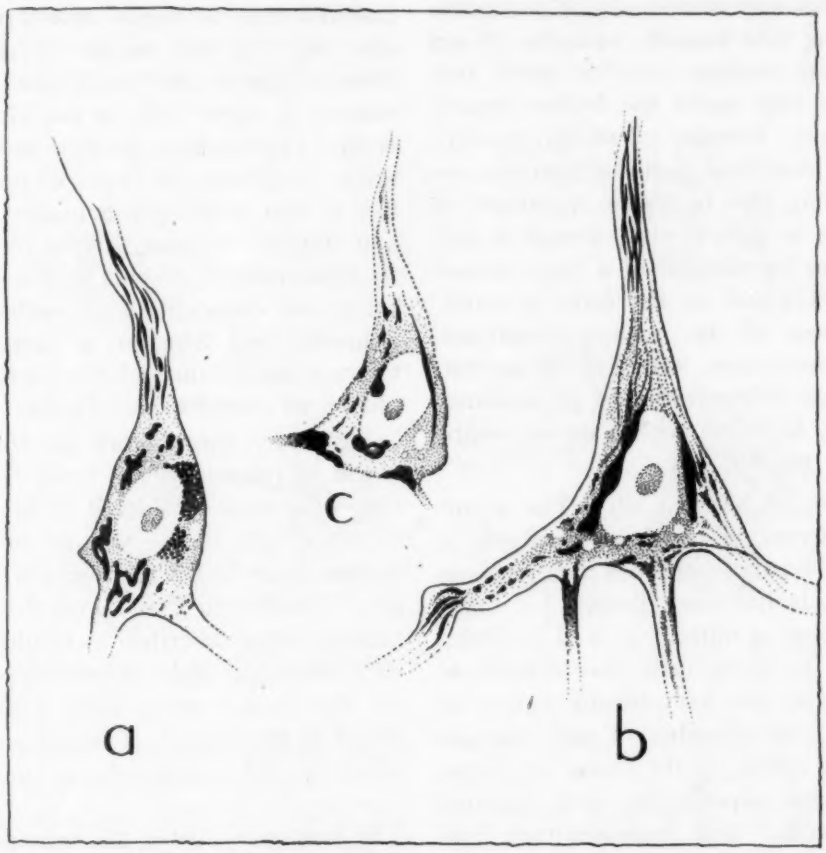

Fig. 11.—Alterations in the neurofibrillar patterns, showing details of fragmentation and granulation (*a* and *c*) and swelling and varicosity (*b*). Cajal's reduced silver stain.

may be present in preliminary stages to complete disintegration with both methods.

Nuclear Changes.—These occur as alterations in the size and shape of the nucleus, the development of vacuoles in its substance and the appearance of certain peculiar alterations in the chromatin elements. The nuclei of regional nerve cells may undergo shrinkage (evidenced by the occurrence of folds in the nuclear membrane), associated with alterations in their shape, as has been pointed out in the general traumatic changes of nerve cells. The nuclei, as well as their nucleoli, may also become eccentric in the simple chromatolytic form of change. In the presence of edema, vacuoles may develop in the chromatin material, forming odd maplike patterns. Even the nucleoli may contain one or more tiny vacuoles, visible only under the higher powers of the microscope. Peculiar chromatin condensations (already described in the section on general changes) may also be found, apparently a general response to injury, even though it may be present within the shadow of a local wound. Degenerative alterations in the form of variability in thickness of the nuclear membrane, rupture of the membrane, with loss of its contents, and ultimate disintegration of its contained structures are to be found with acute traumatic degeneration of the cell.

Multinucleation of Nerve Cells.—The occurrence of what seems to be abortive efforts at cell division on the part of neurons as a response to cortical wounds has been known for many years. The concept of mitotic, as well as direct, nuclear division in nerve cells was introduced by Mondino,[50] who saw karyokinetic figures in these cells about the margins of stab wounds made with a hot needle in the brains of young guinea pigs. These experiments were repeated by Coen,[51] Sanarelli [52] and Tschistowitsch,[53] all of whom found mitotic figures in the nerve cells in the vicinity of the cortical wound. In his observations Friedmann,[54] who studied the reactions to various traumatizing agents in birds, as well as guinea pigs and puppies, noted that karyokinesis was present essentially in its first stages and that this process did not lead to the formation of double cells. This observation was also made by Levi,[55] who stated that mitosis in nerve cells proceeded only through the first phase. That mitosis did occur in nerve cells seems to be clear, as indicated by the drawings of Tschistowitsch, who likewise stated that this phenomenon did not lead to the formation of new nerve cells. It is therefore difficult to account for the conclusions of Vitzou,[56] who asserted that he found new-formed nerve cells and fibers at the margin of resected occipital lobes of pigeons and young apes. Borst [57] found mitoses in nerve cells in the vicinity of foreign bodies (pyroxylin) inserted into the cortex of dogs. Utilizing the factor of irritation, in addition to that of trauma, Schreiber and Wengler [58] and Ranke [59] injected scarlet oil into the brains of experimental animals and were thus able to verify the observations of earlier investigators. Schreiber and Wengler, in particular, were able to trace mitosis through the various intermediate phases to complete cell division.

However, long before all this experimental work on trauma to the brain had been carried out, what was considered to be multinucleation of nerve cells in the vicinity of wounds in the human brain had been observed by Jolly,[37] Tigges,[36] Ceccherelli [38] and Popoff.[39] These observations, being described as incidental, had apparently been lost sight of entirely, however, when we first found nerve cells with two or three nuclei at the margin of recent contusions of the brain, in the course of our initial studies, in

50. Mondino, C.: Nuove osservazioni intorno all' infiammazione traumatica sperimentale del tessuto cerebrale, Gior. d. r. Accad. di med. di Torino **33**:76, 1885; Sulla cariocinesi delle cellule nervose negli animali adulti consecutiva ad irritazione cerebrale, Gazz. d. osp. **6**:107, 1885; Sulla cariocinesi delle cellule del Purkinje consecutiva ad irritazione cerebellare, Arch. di psichiat., sc. pen. ed antropol. crim. **6**:295, 1885.

51. Coen, E.: Ueber die Heilung der Stichwunden des Gehirns, Beitr. z. path. Anat. u. Physiol. **2**:107, 1888.

52. Sanarelli, J.: Die Regenerationsvorgänge an Gross und Kleinhirn, Centralbl. f. allg. Path. u. path. Anat. **2**:429, 1891.

53. Tschistowitsch, T.: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Beitr. z. path. Anat. u. z. allg. Path. **23**:321, 1898.

54. Friedmann: Ueber die histologischen Veränderungen bei den traumatischen Formen der acuten Encephalitis, Arch. f. Psychiat. **18**:284, 1887.

55. Levi, G.: Ricerche sulla capacità proliferativa della cellula nervosa, Riv. di pat. nerv. **1**:385, 1896.

56. Vitzou, A. N.: La néoformation des cellules nerveuses dans le cerveau du singe consécutiva à l'ablation complète des lobes occipitaux, Arch. de physiol. norm. et path. **9**:29, 1897.

57. Borst, M.: Neue Experimente zur Frage nach der Regenerationsfähigkeit des Gehirns, Beitr. z. path. Anat. u. z. allg. Path. **36**:1, 1904.

58. Schreiber, L., and Wengler, F.: Ueber Wirkungen Scharlachöls auf die Netzhaut: Mitosenbildung der Ganglienzellen, Centralbl. f. allg. Path. u. path. Anat. **19**:529, 1908.

59. Ranke, O.: Ueber experimentelle Störung von Differenzierungsvorgängen im Zentralnervensystem, Centralbl. f. allg. Path. u. path. Anat. **21**:385, 1910.

1932.[60] We were quite unaware that any one else had seen them before. The previously reported observations of mitoses in nerve cells in experimental wounds and multinucleation in the margin of old wounds in the human brain were subsequently brought to light by a study of the original contributions on the subject of experimental injury to the brain in general and of the work dealing with evidences of regeneration after injury of the parenchymatous elements of the brain. When Gaupp [61] reported multinucleation of nerve cells at the margin of rather old traumatic lesions of the brain (all sixteen to seventeen years old), he was evidently unaware of this observation by previous students of cerebral injury. Gaupp concluded that this manifestation was a local response to injury of the brain and probably represented an abortive attempt at cell division, although the phenomenon might also be related to a regressive change.

In 1 of our cases many of the nerve cells just a step removed from the fairly sharp margin of a recent contusion of the prefrontal cortex showed evidence of direct nuclear division after a survival period of fourteen days. In some cells this was manifested by an indentation or constriction of the nuclear membrane, a process which was apparently preceded by duplication of the nucleolus. In others the parent nucleus had been completely divided into two daughter nuclei, often with some spatial separation of the two elements (fig. 12). In some individual cells one of the two nuclei showed further evidence of budding; at times a third form was seen. No detectable morphologic change could be seen in the enclosed chromatin material to suggest any specific relationship between this substance and the process of nuclear division.

In a second case, in which the patient survived his injury fifteen days, the process seemed to be somewhat further advanced. In many cells three distinct nuclei were found, all of about the same size and structure. This asymmetric, or eccentric, nuclear division indicated that the regenerative faculty, whatever is the structure in which it is resident, was not equally spread throughout the original nucleus but was usually transmitted in greater part to one of the two daughter nuclei. These cells seemed to be situated somewhat closer to the margin of the contusion than the cells in the first case, but this is perhaps without significance. The individual cells also showed more evidence of regressive change, both as to the cytoplasm of the cell and the nucleus. After three weeks, four nuclei were only occasionally observed.

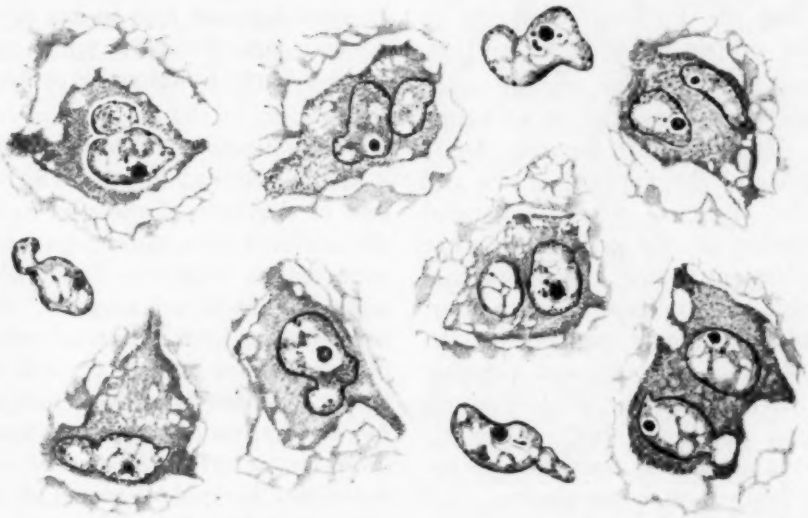

Fig. 12.—Multinucleation of nerve cells at the margin of a contusion. Hematoxylin and eosin stain; survival period, fourteen days.

Multinucleation of nerve cells was observed also in cases with survival of twenty-one days (contusion), thirty-eight days (laceration) and seven months (intracerebral hemorrhage). This would indicate either that the process, once begun, was continued over a long period or that the cells so altered remained in this state for a long interval. The occurrence of a considerable degenerative change in the cells so affected seemed to indicate that these cells were destined soon to undergo complete dissolution; by analogy, one might presume that the remaining

60. Rand, C. W., and Courville, C. B.: Multinucleation of Cortical Nerve Cells at the Margins of Traumatic Lesions of the Human Brain, to be published.

61. Gaupp, R.: Zweikernige Ganglienzellen im traumatischen Hirndefekten, Ztschr. f. d. ges. Neurol. u. Psychiat. **149**:122, 1934.

cells in the vicinity of these traumatic lesions sooner or later might be affected by the process, which seems simply to be a prelude to their effacement. As Gaupp [61] has pointed out, this process may be observed as late as seventeen years after the injury.

As a study of the occurrence of multinucleation in older traumatic lesions of the brain, we undertook the investigation of the reaction of nerve cells in the vicinity of old contusions of the brain in 10 consecutive cases which have come to our attention in the Cajal laboratory. Nerve cells with two, sometimes three, nuclei were found at the margin of the lesions in every case. This observation would suggest that the response is not a rare and incidental change but one of the characteristic reactions to injuries of the cerebral cortex. It was not present in a case of an old contusion of the cerebellar cortex, suggesting that the Purkinje elements do not have a similar propensity in this direction.

These evidences of regressive change were both acute and necrobiotic, as well as subacute, and even chronic. In addition to the irregularity of the cell margin and the rupture of the cell membranes of the nucleus, which suggested prospective dissolution of the cell, there were in evidence vacuolation of the cytoplasm and nucleus, suggestive of advanced edematous change, and abundant lipoidal pigment in the cytoplasm (indicative of a local, and possibly vascular, change, in view of the relative youth and short survival period of both patients). These changes were associated ones, due to the injury or to its immediate consequences, and were not specifically related to the process of nuclear division.

When these observations are reviewed in the light of the presence of only two-nucleated cells at the margins of older cerebral wounds, the possibility is suggested that this further ability to division of one of the daughter nuclei is limited to the acute phases of the injury, a process which may be stimulated by the presence of decadent material, which is presumed to serve as a chemical stimulus to the regenerating activities of the interstitial cells. It is also possible that this process of nuclear division is a continuous one, which may persist for weeks or months after the injury has been sustained. The only alternative to this conclusion is to assume that these binucleated cells are capable of survival for considerable intervals, a conclusion which is of doubtful validity because of the presence of advanced degenerative changes obviously present in the affected cells. While in some instances what seems to be an initial effort at cellular (as well as nuclear) division is found in the form of local indentation of the cell body, at times with some early alterations in the conformation of the cell, no positive evidence that actual cell division did occur was observed. This would conform to the conclusions made by investigators who have observed mitotic figures after experimental trauma to the effect that such abortive efforts did not lead to the complete formation of new nerve cells.

In the case of multinucleation of human nerve cells in response to local injury, it must therefore be concluded that these alterations are but the latent manifestations of the potency of the cell, not entirely static, which leads to incomplete (abortive) cell division. The process is limited to nuclear division, with possible minor morphologic evidence in the direction of division of cellular cytoplasm as well. Obviously, the process does not lead to any physiologic restoration; in fact, the cell in which the process occurs is very likely functionally useless, if not actually dead.

Ferrugination ("Calcification") of Nerve Cells.—Although "calcification" of nerve cells was one of the first of the types of cellular change to be noted as a consequence of trauma, being reported as such by Virchow [35] in 1857, and subsequently noted anew by Friedlander, it is by no means limited to traumatic lesions. Ernest also saw them about cortical wounds. Spielmeyer [62] stated that this change is found commonly in areas of softening secondary to arterial occlusion or other circulatory disorders, as well as in old encephalic foci and in the region of abscesses. He observed it in cases of dementia paralytica, especially of the juvenile variety, in which the Purkinje cells of the cerebellum may be so altered. These cells may also be affected in degenerative atrophies of this organ. Freeman [63] has shown a large group of such cells in the margin of an old wound of the brain.

For many years the dark coloration of these cells led to the belief that these cells were calcified, but more recently it has come to be recognized that they are actually encrusted with iron. Moreover, it has also come to be recognized that the process, while chronic in its duration, may take place in relatively recent lesions. For example, Cajal [15] found this process taking place in nerve cells not far removed from the margins of experimental wounds in the brain after four-

62. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, pp. 43, 44 and 456.

63. Freeman, W.: Neuropathology: The Anatomical Foundation of Nervous Diseases, Philadelphia, W. B. Saunders Company, 1933, pp. 25 and 26.

teen days, although it had apparently reached its climax between the twentieth and the twenty-fifth day.

This change in the nerve cell is obviously not primarily traumatic, since it is found in so many other conditions. The presence of such alterations so typically at the margins of areas of softening due to vascular obstruction suggests that deprivation of oxygen is probably at the basis of the process. This is suggested by the observation of many such cells in areas of cortical softening due to asphyxia, as found in cases after a suitable interval of survival (Courville [48]). The presence of such cells at the margin of old cortical scars is a common observation and is probably to be accounted for by the disruption of the local circulation as an effect of disorganization of the regional nerve tissue by the contusion or laceration.[64]

These iron-encrusted cells (they are beautifully demonstrated with the prussian blue method) are usually found in small groups in the cortex at the margin of defects consequent to old contusions. Sometimes a considerable number of such cells may be found within a limited area; at other points only one or two scattered elements are to be seen. The cells are small and shrunken and stain a deep blue with hematoxylin. If a group of them are found together, they are more closely approximated than are normal nerve cells, and it is suggested that this is due to absence of the interstitial tissues, which had disintegrated as a result of lack of oxygen. The atypical position of individual cells also indicates that some disorganization has taken place.

Even with higher magnifications, there is little detail of the cell to be made out. At times the site of the nucleus is evident by a central pale area. Otherwise, the cells stain a uniform or mottled pinkish lavender to a deep bluish purple; close inspection shows small nodulations on the cell body and its processes. These apparently represent small masses of iron, which may be few, or, at the opposite extreme, may completely cover the cell. Because of the definiteness with which these cells are demonstrated, the proximal portions of the major cell processes are also well shown. They are frequently broken off ("fractured"), with sharp edges, suggesting that this process has made the cells brittle in texture. The small size of the cell, its shrunken appearance and the tortuosity of its apical dendrite suggest, further, that in the process the affected cells may have gone through the sclerotic type of change (fig. 13).

These cells are obviously dead and in this mummified condition are capable of survival for many years. It is for this reason that they are found so typically in the margin of old scars.

Summary.—Local changes in nerve cells follow a variety of patterns, which are dependent not only on the original traumatizing force but on a number of circulatory changes which follow in the train of the injury—hemorrhage, edema, ischemia and probably some degree of local anoxemia. These changes are therefore reminiscent of the alterations in ganglion cells which follow other pathologic processes, except for the interesting observation that evidences of multiple types of change may be found within a single cell.

From a practical standpoint, it is realized that cells which are engulfed in the general debris of the area of disintegration are immediately destroyed and all trace of them is gone forever. Moreover, the cells within a bordering zone of destruction are immediately killed, although their identity may be maintained for several days by the process of "preservation," the result of action by some antiautolytic substance diffused through the adjacent tissues from the blood plasma of the local clot. Other dead cells fade out of the picture usually within a short time ("ghost cells"); still others undergo a slower process of active traumatic disintegration, perhaps the most characteristic of all the traumatic changes. Distal to this bordering zone are cells which are affected by various types of change, which are to a great extent reversible. In some cases at least with a survival period of two weeks or more, the nerve cells make an abortive attempt at regeneration, as indicated by the direct division of the nucleus into double or triple daughter nuclei. The cells themselves apparently do not divide. Evidences of this abortive reaction may be found months or years after the injury.

It seems likely that some cells may persist but with an abnormal function, an assumption based on the occurrence of epileptiform convulsions which have their origin in groups of cells at the margins of old wounds which discharge abnormally according to the electroencephalogram. The physical counterparts of this abnormal physiologic activity could not be determined from the material available for the present study.

GENERAL CONSIDERATIONS

In the investigation of this series of alterations in nerve cells which result from the general, as well as the local, effects of injury, certain facts

64. Rand, C. W., and Courville, C. B.: Iron Encrustation of Nerve Cells in the Vicinity of Traumatic Lesions of the Cerebral Cortex, Bull. Los Angeles Neurol. Soc., to be published.

have become apparent. In an effort to evaluate these changes in the light of clinical observations, some fundamental considerations, as discovered by these studies, will be briefly outlined.

1. Death of an injured nerve cell may be immediate or delayed. If death of the cell has come as an immediate effect of the injury and the cell lies within the area of destruction, it may undergo immediate disintegration in the damaged nerve tissue, its remains being completely obscured by the attendant hemorrhage. If the dead cell happens to be at the margin of this area, it may persist with relatively no morphologic alteration for a week or more, owing to the action of some antiautolytic ferment which is present in the blood plasma ("preservation" necrosis of Cajal). Still other dead cells quite promptly fade out of the picture *en masse,* being found as "ghost forms" within a few hours after the injury, and are thought to disappear within a few days, although an occasional cell of this type is still found after five weeks. The last group of dead cells undergo, sooner or later, progressive structural degenerative changes, which may be described as progressive traumatic disintegration.

2. Most cells outside the area of primary destruction and the bordering zone of secondary destruction are able to survive the shock of injury, although death may overtake them later. These cells may show either local or general effects of injury. Local effects may be evident in nuclear change, damage to a certain portion of the cell or loss of some of its processes. The entire cell may also be affected, as manifested by loss of tigroid substance shrinkage, certain physicochemical changes in its cytoplasm or infiltration of hematogenous pigment. It is believed that these changes are not necessarily fatal but may be recovered from if no other pathologic process adds insult to the injury. This physical recovery of an injured cell has been appropriately termed "reversible reaction."

3. It is also possible that some cells may survive in an injured state so that they are no longer of any value to the organism's economy. Not only may such cells contribute nothing to the normal functioning of the brain, but they may be the source of abnormal electric discharges responsible for post-traumatic convulsive seizures.

4. Through a peculiar provision of nature, dead, as well as crippled, cells may be preserved for months or years by being encrusted with iron (ferrugination, often miscalled "calcification"). Such cells are commonly found at the margins of old contusions and lacerations of the brain. Their death, however, is probably due to an attendant circulatory disorder (anoxemia), since they have been found with many other lesions, especially with softening due to vascular occlusion and after asphyxia.

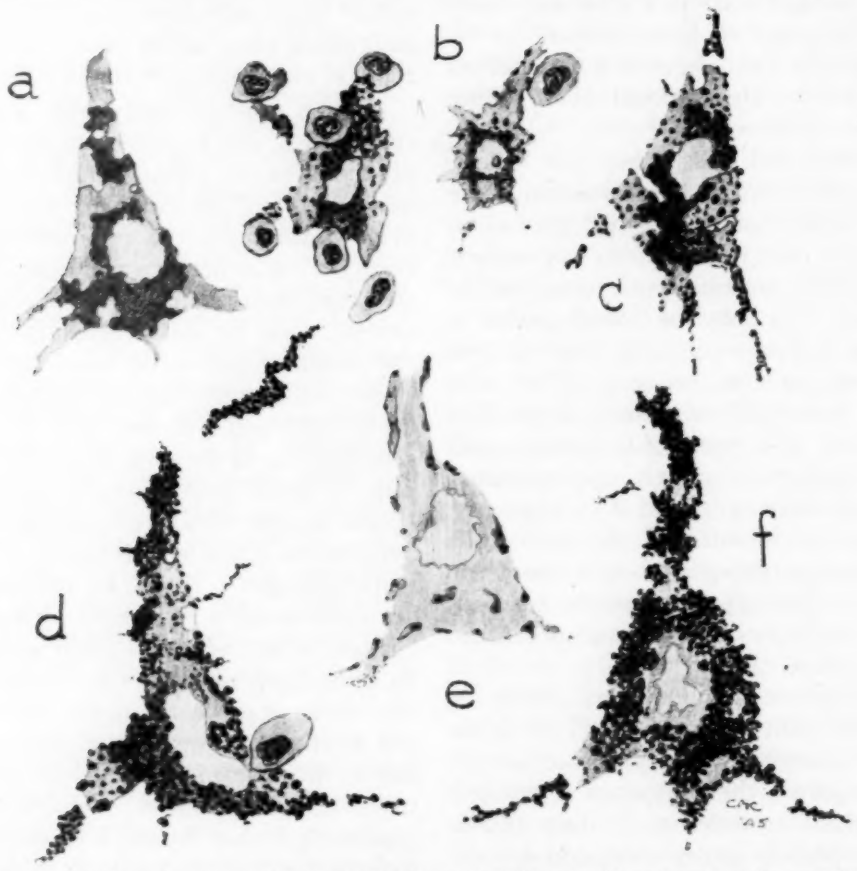

Fig. 13.—Iron encrustation of nerve cells (ferrugination; "calcification") as found at the margins of old contusions of the cerebral cortex. (*a*) Preliminary stage, before iron is deposited; (*b*) early stage, showing presence of phagocytes engulfing broken processes of cells (dendrophagocytosis); (*c, d* and *f*) various degrees of encrustation; (*e*) "ghost form," in which the scarcely visible cell is outlined by granules of iron. Hematoxylin and eosin stain.

5. In all these changes, it has been observed that there is an individual susceptibility to injury, as to any other disease process. In a group of nerve cells, one cell may be found to undergo immediate dissolution (as a "ghost form") or to show severe effects of damage, while

the other cells may be morphologically intact. It is assumed that this variable susceptibility to pathologic processes is due to the particular state of the metabolism of the cell at the moment of injury.

6. It is likely that the speed with which the destructive process affects the cell has something to do with its appearance at the time it is studied. While there are exceptions to this rule (i. e., preservation necrosis), other things being equal, regressive changes will be more prominent and sooner terminated adjacent to the local cortical lesion than at a little distance from it, even though the cells in both areas are ultimately destined for destruction.

7. A single cell may present evidence that more than one necrobiotic process may be affecting its structure. It has been pointed out that as a general effect of craniocerebral injury, nerve cells of the cortex may show both loss of stainability (presumed to be due to the shocking effects of the injury) and the occurrence of cytoplasmic (rare), perinuclear, intranuclear or even nucleolar vacuolation (suggesting the action of cerebral edema). In reaction to local wounds, these combined effects are even more evident. Pyknotic (or sclerotic) change, for example, may be found in a cell which also shows the effects of preservation necrosis, pigmentary infiltration, ischemia, edema or even acute traumatic degeneration (cytoplasmic vacuolation with disintegration of the cell membrane). This combination of abnormal changes makes it difficult at times to classify categorically the nature of cellular change.

8. The multiplicity of changes possible in nerve cells, or in even a single cell, makes it evident that such alterations are due not only to the original shocking force of the injury but to the attendant hemorrhage, impaired circulation (ischemia with consequent anoxemia) and edema.

9. Not only do death and injury of nerve cells occur as an immediate effect of the injury, but, in addition, progressive change may take place in nerve cells as a result of processes which are initiated by the injury and which continue for a variable time thereafter. This is true to some extent even in the case of simple wounds (puncture wounds or contusions) but is much more evident with extensive lacerations of the brain, such as follow gunshot wounds. The exact cause of these phenomena in simple wounds is not clear, but it is presumed to be minor local changes in the circulation and the formation of the regional scar. This seems to be more definitely the case with lacerations, in which contraction of the central scar appears to result in intermittent vascular spasm with local ischemia and cell injury or death. As an immediate evidence of this progressive change even in recent injuries, one may find that a cell which has begun to react from the effects of injury is being overtaken by degenerative changes.

10. Multinucleation of nerve cells, which is found as early as two weeks after the initial injury is sustained and which may be evident at the margins of cortical lesions many years old, is a process which indicates an inherent recreative ability in elements which are generally considered to be biologically static. This process is incomplete and eccentric and does not lead to useful regeneration of nerve cells.

11. There is as yet no definite way of determining the degree of normal function resident in a nerve cell on the basis of its physical structure. There seems to be some relationship between the severity of the general effects of injury and the amount of Nissl substance still resident in the cell at the time of examination, but whether this change is entirely to be accounted for on the basis of the initial shock of the injury, or whether it is due in part at least to other attendant situations, cannot be stated with certainty. Marked changes of the same degree as a result of local injury have been found apparently to be responsible for abnormalities in the electric discharge from the region, as determined electroencephalographically.

12. It is as yet unsafe to say that a normal morphologic condition is always an indicator of normal function. It is therefore possible that abnormal electric discharges responsible for post-traumatic epilepsy may have their origin in cells which to all appearances are structurally normal. Determination of the facts in this situation is outside the realm of neuropathology, as an isolated science, at least with the diagnostic facilities now at hand. It may well be that facts of importance in this field can be learned if the pathologist will work in conjunction with the physiologist, making a comparative study of the structural changes in the nerve and the nature of electric discharges, as determined electroencephalographically.

These general considerations as to the histologic alterations in cortical nerve cells which occur in consequence of focal traumatic lesions are found to apply in many respects to the other cellular elements as well. In this sense, the traumatic changes in nerve cells tend to follow a general pattern: They may be immediately destroyed; they may undergo subsequent (delayed) dissolution; they may be seriously damaged and persist in crippled form, or they may sustain only minor injuries, from which they may recover (reversible reaction). The specificity of the changes in nerve cells are based on their different inherently functional character, their great susceptibility to noxious influences and, in particular, their difference in structure. The highly specialized function of the ganglion cells, their greater delicacy of structure and their inability to react by reproducing themselves in the presence of necrobiotic processes, account, in the last analysis, for the current, as well as the ultimate, histologic picture that these cells present in the cortex which has been subjected to physical damage.

SUMMARY AND CONCLUSIONS

As a result of craniocerebral trauma, certain changes may result in the structure of the cortical nerve cells of the cerebrum and cerebellum. These changes may be general, as a result of shock of the original traumatizing force (chromatolysis) or consequent to the generalized edema (vacuolation) which so often follows such injuries in civilian life. More noteworthy, because of their variety and degree, are those alterations which are the direct result of focal injuries of the cortex. Among the various local cellular reactions may be named preservation necrosis (retention of normal structure by dead cells);

pigmentary infiltration (which is found in the vicinity of traumatic cortical hemorrhages); pyknotic, ischemic or sclerotic change and lipoidal degeneration (all resulting from local circulatory disturbances); a modified edematous change (incident to local edema following contusion or laceration); acute traumatic change (which may occur in the form of acute traumatic chromatolysis); acute total disintegration (ghost cells) or acute progressive necrosis; multinucleation of nerve cells (evidence, presumably, of an abortive attempt at regeneration), and, finally, ferrugination (wrongly designated by some as "calcification"), a process by which a dead cell may remain among the living as a mummified relic for many months or years.

The occurrence of definite and widespread chromatolytic changes in the nerve cells, which may persist for some time before reversible change takes place, furnishes a possible basis for the persistent psychic residual disturbances which so often follow craniocerebral injury. Local changes in nerve cells observed at the margin of regional traumatic injuries of the cerebral cortex not only furnish an explanation of the deficit pictures which result from loss of functioning areas but probably are responsible for residual convulsive seizures. The possible physical counterparts of abnormal discharge of electric current responsible for such seizures could not be determined in this study, concerned as it was largely with cases of craniocerebral injury with relatively short periods of survival.

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DISTURBANCES IN SLEEP MECHANISM: A CLINICOPATHOLOGIC STUDY

III. LESIONS AT THE DIENCEPHALIC LEVEL (HYPOTHALAMUS)

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In contrast to the questionable effect of cortical lesions on the sleep mechanism, it is well known that discrete diencephalic lesions, especially in the hypothalamus, are accompanied with disturbances in sleep. There is a wealth of clinical and experimental evidence that the hypothalamus acts as a sleep-regulating center. Conclusions regarding the relationship of anatomic lesions in the hypothalamus to precise disturbances in function should be made with reservation, because areas adjacent to the hypothalamus, such as the thalamus and the basal ganglia, may also be involved by compression or edema. We wish to emphasize that in many of the reported cases, as in some of ours, the lesions were widespread. The 17 cases to be described and the recently recorded experimental data of Harrison, Magoun and Ranson[1] may help in the clarification of these intricate problems. We shall attempt to demonstrate that in a few of our cases the hypothalamus was involved to the exclusion of the thalamus and the basal ganglia, whereas in most of the other cases such exclusion could not be shown. Only in a few of our cases could involvement of specific portions of the hypothalamus be related to disturbances in sleep.

REPORT OF CASES

CASE 1.—*Adamantinoma of the third ventricle with involvement and destruction of most of the hypothalamic nuclei. Endocrine disturbances: hyperthermia; ocular manifestations and insomnia, followed by somnolence. Increased intracranial pressure.*

S. P., a woman aged 45, experienced dimness of vision. Within a period of one and a half years she gained 70 pounds (31.8 Kg.); she slept poorly and later became drowsy. The menopause occurred at the age of 39.

Neurologic Examination.—Examination disclosed pallor of the optic disks and sluggish pupillary reactions to light and in accommodation. The left palpebral fissure was larger than the right. There were bilateral ptosis, palsy of the right third nerve and hyperthermia.

Laboratory Data.—The spinal fluid was clear and contained no cells. The Pandy reaction was faintly positive, and the initial pressure was 140 mm. of water. The basal metabolic rate, determined on two occasions, was — 13 and — 17 per cent. The blood chemistry was normal.

Autopsy.—Two small adamantinomas replaced the floor of the third ventricle (fig. 1). The entire hypothalamic region was studied serially. Practically all the nerve cells of the hypothalamic nuclei in the preoptic, supraoptic and infundibular regions, especially on the right side, were destroyed and showed all types of pathologic changes. The nuclear masses involved were the medial and lateral preoptic areas, the lateral hypothalamic area, the lateral tuberal nuclei, the right nucleus supraopticus, nucleus paraventricularis, nucleus suprachiasmaticus, nucleus supraopticus diffusus, nucleus hypothalamicus ventromedialis and nucleus hypothalamicus dorsomedialis, the anterior and dorsal hypothalamic areas and the perifornical area. The visible ganglion cells of the various hypothalamic nuclei showed absence of pigment and chromatin granules, homogenization or complete destruction. The nerve cells in the mamillary nuclei appeared normal. The thalamus and the basal ganglia, except for the left corpus Luysi, were normal.

Comment.—The insomnia, followed by drowsiness, was undoubtedly the result of partial destruction of the anterior and posterior hypothalamic nuclei by the adamantinoma. It seems

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A report on the study, of which the present paper is the third section, was made before the Chicago Neurological Society on May 20, 1943, and before the New York Academy of Medicine, Section of Neurology and Psychiatry, on Feb. 8, 1944. An abstract of the paper, with discussion, appeared in the January 1945 issue of the ARCHIVES, page 79.

1. Harrison, F.; Magoun, H. W., and Ranson, S. W.: Some Determinations of Thresholds to Stimulation with Faradic and Direct Current in the Brain Stem, Am. J. Physiol. **121**:708, 1938.

reasonable to assume that the initial symptoms of insomnia were caused by the lesions in the rostral hypothalamic region. Later, with involvement of the caudal portion of the hypothalamus, somnolence appeared. There were also some ocular manifestations, such as bilateral ptosis and paralysis of the right third nerve. The dilated ventricles were considered the result of increased intracranial pressure.

CASE 2.[2]—*Angioma of the hypothalamus, extending from the rostral part of the supraoptic region to the mamillary bodies. Polyuria, polydipsia, hypothermia, endocrine disturbance, ocular manifestations and somnolence. Increased intracranial pressure.*

M. R., a man aged 31, had suffered bilateral progressive loss of vision; this condition had gradually improved. During the past thirteen years he had slept a great deal and was drowsy most of the day but could easily be awakened.

Neurologic Examination.—Examination disclosed bilateral anosmia, atrophy of the optic nerves and left homonymous hemianopsia. Convergence was defective in the left eye. The left palpebral fissure was wider than the right. During his stay in the hospital the patient had a consistently low temperature, ranging from 97.6 to 90 F., and slept most of the time.

Laboratory Data.—The cholesterol of the blood measured 177 mg. and the urea nitrogen 9.9 mg., per hundred cubic centimeters. The spinal fluid was clear and under an initial pressure of 180 mm. of water. Tests for globulin gave a slightly positive reaction. The urine was normal. The basal metabolic rate, determined at various periods, was —36, —43 and —23 per cent.

Autopsy.—There was a tumor between the floor of the third ventricle and the sella turcica, extending from the optic nerves to the mamillary bodies (fig. 2). Practically the entire floor of the third ventricle was destroyed by the neoplasm. Serial sections through various hypothalamic regions revealed that most of the nerve cells of the hypothalamic nuclei had undergone pathologic changes. This was especially true in sections through the nuclei in the supraoptic and infundibular regions. In the mamillary region, the supramamillary area, the medial and lateral mamillary nuclei, the lateral hypothalamic area, the nucleus intercalatus and part of the substantia grisea centralis were destroyed. The right mamillary body was more involved than the left (fig. 2 *E*). The thalamus and the basal ganglia appeared normal.

Comment.—Although the entire hypothalamus was involved, the hypersomnia was apparently secondary to destruction of the caudal part of the hypothalamus, affecting the lateral hypothalamic nuclei in that region.

CASE 3.—*Neuroblastoma of the most caudal part of the hypothalamus and the aqueduct of Sylvius. Endocrine disturbances, hypothermia, ocular manifestations and reversal in sleep mechanism. Increased intracranial pressure.*

B. M., a woman aged 23, gave a history of gain in weight, tendency to hirsutism, attacks of vertigo and falling, blindness in the right eye and diminished vision in the left eye.

Neurologic Examination.—Examination disclosed bilateral secondary atrophy of the optic nerve; dilatation of the pupils, the left being larger than the right, with absence of the reaction to light but with a slight reaction on convergence; incomplete ptosis on the left side, and partial ptosis on the right; slight bilateral weakness of the external rectus muscle; failure of convergence of the right eye, and impairment of upward gaze of the left eye. The patient slept poorly, was inattentive and frequently rubbed and scratched her nose. During the day she was frequently drowsy and slept but could be aroused. At night she was unable to sleep. In addition, she had hypothermia.

Fig. 1 (case 1).—Adamantinoma destroying the floor of the third ventricle and part of the hypothalamic nuclei.

Laboratory Data.—The urine showed a faint trace of albumin. The blood pressure was 112 systolic and 80 diastolic. The blood chemistry was normal. The spinal fluid was clear and contained 1 cell per cubic millimeter. The Pandy reaction was negative. The initial pressure was 360 mm. of water.

Autopsy.—A section through the most caudal part of the third ventricle revealed a neuroblastoma which impinged on the posterior wall of the left side of the third

2. This case was described in detail from the point of view of disturbances in temperature in a previous publication (Davison, C., and Selby, N. E.: Hypothermia in Cases of Hypothalamic Lesions, Arch. Neurol. & Psychiat. **33**:570 [March] 1935).

ventricle, close to the aqueduct of Sylvius (fig. 3). The latter was constricted and obstructed by the tumor (fig. 3). The hypothalamus and the mesencephalon were studied serially. Sections through the preoptic, lateral supraoptic and infundibular regions of the hypothalamus were normal except for congestion of the vessels. Occasional ischemic changes and chromatolysis were present in the nerve cells of the lateral hypothalamic area of the caudal infundibular region. A section through the most caudal part of the mamillary region disclosed extensive destruction and pathologic changes in the nerve cells of the lateral mamillary nuclei and the lateral hypothalamic area, particularly on the left side. The thalamus and the basal ganglia were normal.

Fig. 2 (case 2).—Coronal sections of the brain. *A*, section through the preoptic region, showing a tumor invading the right side only; *B*, section through the rostral part of the supraoptic region, showing the tumor invading the oral part of the paraventricular nucleus; *C*, section through the beginning of the infundibular region, showing the tumor invading and destroying the ventromedial, tuberal, supraoptic and lateral hypothalamic nuclei; *D*, section through the middle of the infundibular region, showing the tumor invading and destroying the tractus supraopticus and ventromedial part of the posterior, dorsal and lateral hypothalamic areas; *E*, section through the anterior part of the mamillary region, showing the tumor invading and destroying the nerve cells of the nuclei intercalatus, the nuclei mamillaris medialis and lateralis, the supramamillary area, the right fasciculus mamillothalamicus and the lateral hypothalamic area, and *F*, section through the posterior part of the mamillary region. The mamillary bodies could be identified at this level; there is destruction of the right mamillary body. The nerve cells of the mamillary nuclei and the lateral hypothalamic areas showed pathologic changes at this level.

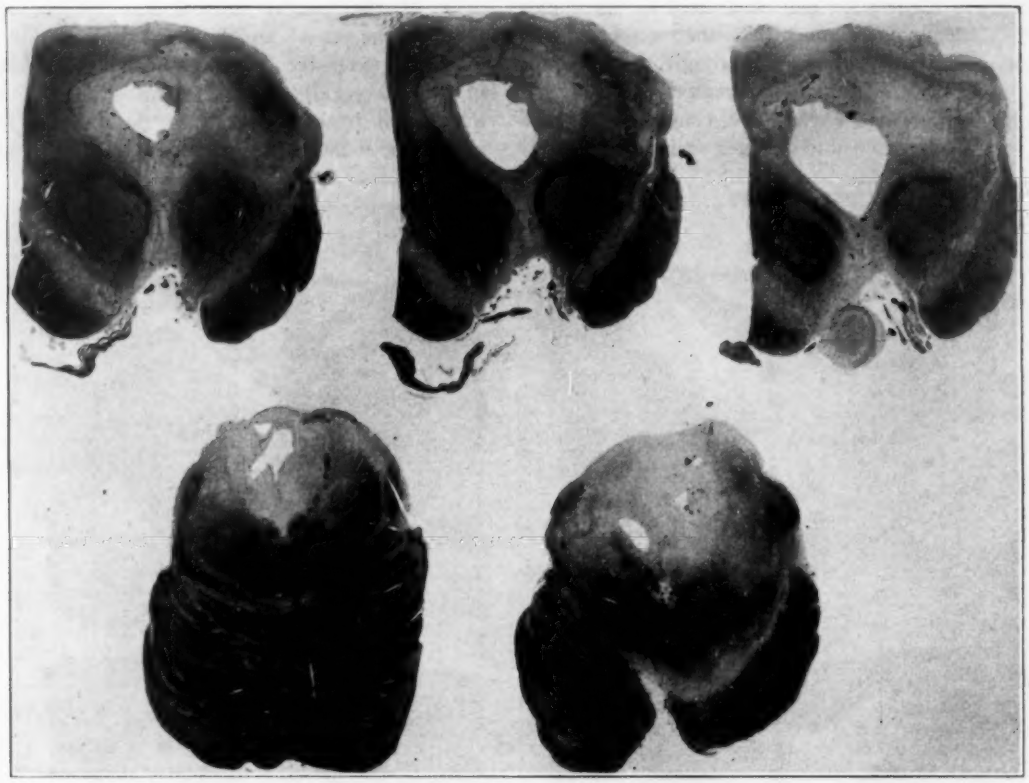

Fig. 3 (case 3).—Neuroblastoma of the caudal end of the hypothalamus and the rostral part of the mesencephalon.

Fig. 4 (case 4).—Colloid tumor of the third ventricle; compression of the hypothalamus.

Comment.—The disturbance in sleep mechanism was undoubtedly the result of involvement of the caudal region of the hypothalamus. Additional points of interest in this case were the reversal of sleep rhythm and the involvement of the nuclei of the ocular nerves.

CASE 4.—*Colloid tumor of the third ventricle; compression and partial destruction of the hypothalamus.*

especially the anterior and middle thirds; somnolence. Increased intracranial pressure.

M. J., a girl aged 9 years, suffered from frontal headaches and lethargy, from which she could be aroused.

Neurologic Examination.—There were lateral deviation of the eyes, absence of the knee jerk and a bilateral Babinski sign. The patient died a few hours after a spinal tap.

Laboratory Data.—The spinal fluid was stated to be under slightly increased pressure; there were traces of globulin and 67 lymphocytes per cubic millimeter.

CASE 5.—*Carcinoma of the lung with metastases to the hypothalamus, thalamus and cerebral peduncle on the left side. Hemiplegia oculomotorius alternans; somnolence. Increased intracranial pressure.*

R. L., a woman aged 39, had a carcinoma of the lung. Eight months after appearance of the pulmonary signs, there developed paralysis of the right side of the body, blurring of vision, drooping of the left lid, right internal strabismus and attacks of somnolence, from which she could be aroused.

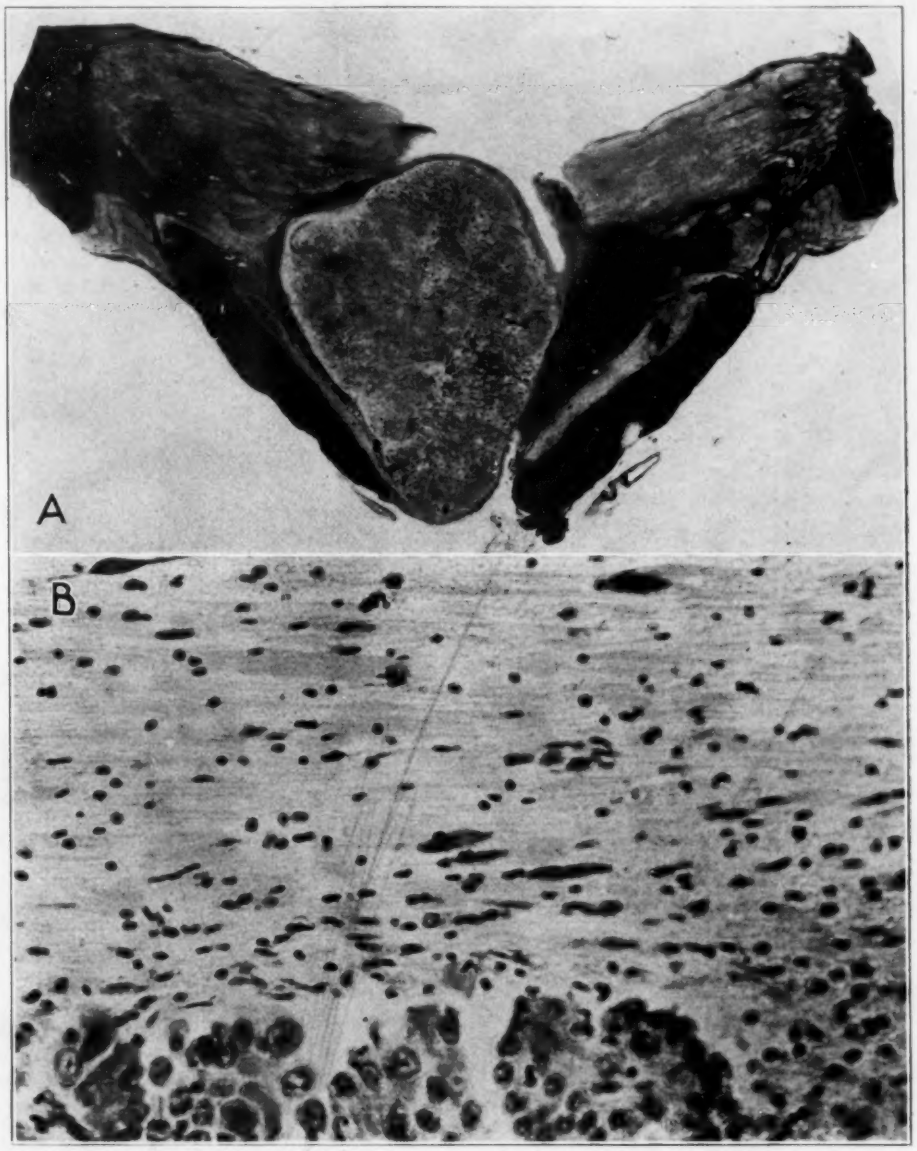

Fig. 5 (case 5).—*A,* metastatic carcinoma in the caudal part of the left hypothalamus, with compression of the right hypothalamus; *B,* diminution in number, extreme shrinkage and pyknosis of the hypothalamic nerve cells.

Autopsy.—A colloid tumor filled the slightly dilated third ventricle and compressed the hypothalamic nuclei (fig. 4). The various nerve cells of the hypothalamus, especially in the anterior and middle thirds, disclosed shrinkage, chromatolysis, disappearance of pigment granules and occasional pyknosis. Although the posterior part of the hypothalamus was free from tumor, the nerve cells showed loss of chromatin and iron pigment with occasional disintegration.

Neurologic Examination.—Examination disclosed flaccid hemiparesis with hyperreflexia and pathologic reflexes on the right side; paralysis of the left third nerve; paralysis of upward gaze, and paralysis of the right side of the face of central type. The right pupil was smaller than the left.

Laboratory Data.—Studies of the spinal fluid were not recorded. The urine and the blood chemistry were normal.

Autopsy.—A metastatic tumor in the left caudal hypothalamic region (fig. 5 *A*) compressed the medial nucleus of the thalamus, the substantia nigra, the corpus Luysi, the cerebral peduncle and the third nerve on that side (fig. 5 *A*). The tumor also extended into the mesencephalon as far as the superior part of the fourth ventricle. The posterior third of the left hypothalamus was almost completely destroyed. The surviving nerve cells showed all types of pathologic changes, such as diminution, shrinkage and pyknosis (fig. 5 *B*). The nerve cells of the right hypothalamic nuclei exhibited ischemic changes and chromatolysis.

Comment.—This case presented the classic picture of Weber's syndrome and somnolence as a result of invasion of the posterior part of the hypothalamus by the tumor. The influence of the thalamus and the basal ganglia cannot be completely ruled out because of compression.

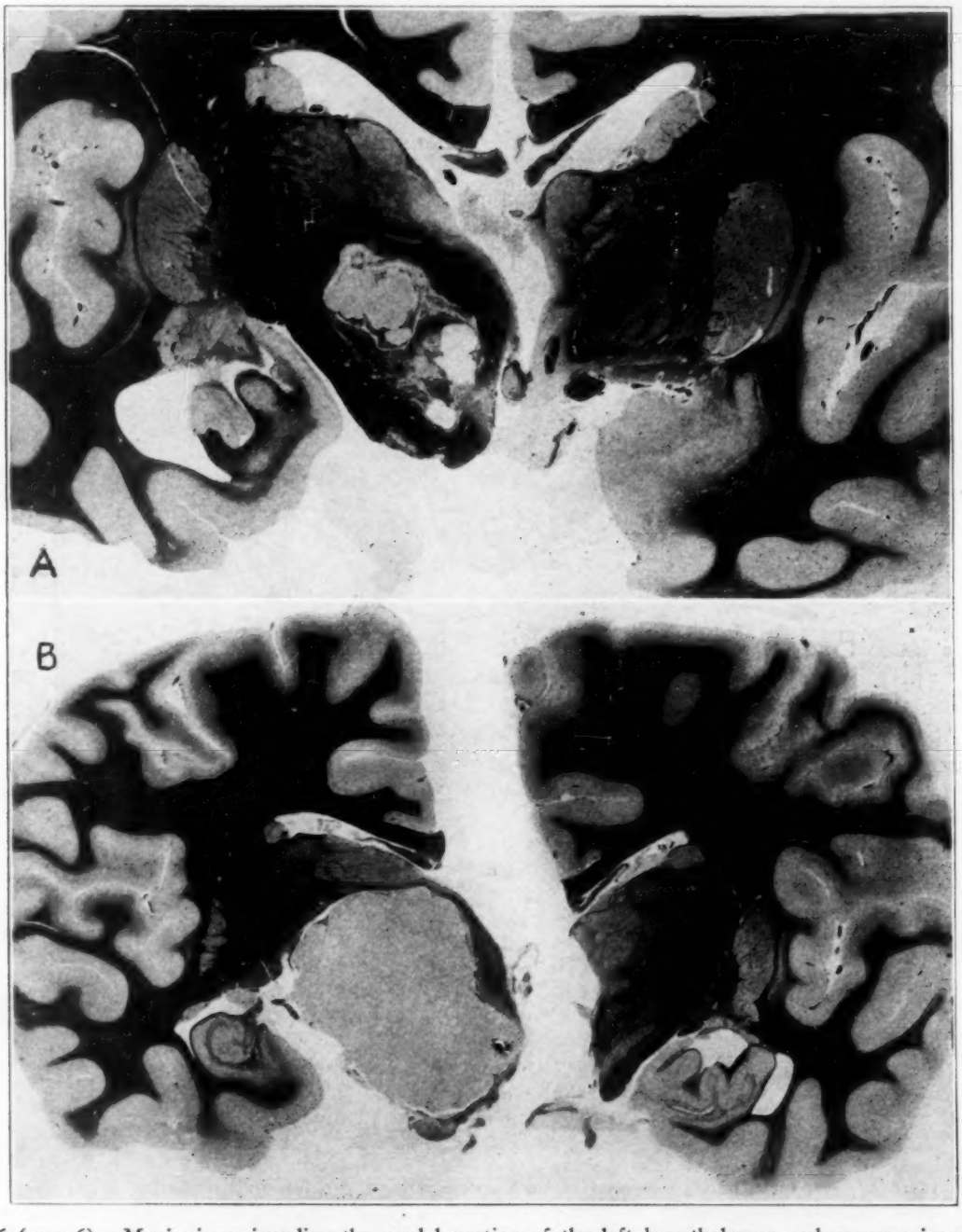

Fig. 6 (case 6).—Meningioma invading the caudal portion of the left hypothalamus and compressing the diencephalon. Notice also the compression of the opposite hypothalamus.

CASE 6.—*Meningioma of the base of the brain, invading the caudal part of the left hypothalamus, with compression and destruction of the right hypothalamus. Ocular manifestations, hyperthermia and somnolence. No evidence of increased intracranial pressure.*

B. S., a man aged 52, had so-called influenza for ten days, associated with fever during that period, followed by lethargy, drowsiness and stupor, from which he could be aroused.

Neurologic Examination.—Examination revealed pathologic laughing and crying, spastic right hemiplegia, parkinsonian facies and sluggish pupillary responses to light and in accommodation. Lack of convergence, impairment of movements on upward, downward and lateral gaze, nystagmus and paresis of the right side of the face of central type were also present.

Laboratory Data.—Spinal tap revealed a normal status; pressure readings could not be carried out successfully because of the forced laughing and crying. The urine and the blood chemistry were normal.

Autopsy.—A meningioma was found at the base of the brain between the left hippocampus and the left peduncle (fig. 6). The tumor invaded and compressed the following structures on the left side: the hypothalamus, the inferior parts of the medial and lateral thalamic nuclei, the corpus Luysi, the substantia nigra, the cerebral peduncle and the mamillary body (fig. 6 *A*). Practically the entire left side of the mesencephalon was compressed in the region of the aqueduct. Sections through the supraoptic region showed destruction of the left nucleus supraopticus, part of the left paraventricular nucleus and the left lateral and anterior hypothalamic areas, with pathologic changes in the nerve cells. In sections through the posterior part of the third ventricle, the tumor invaded and destroyed the greater part of the ventromedial and dorsomedial hypothalamic nuclei on the left side and the lateral, dorsal and posterior hypothalamic areas, the mamillary nuclei and the nucleus intercalatus on the same side (fig. 6 *B*). The nerve cells of these masses on the left side showed pathologic changes, but those on the right side were normal. In sections through the aqueductal region, there were distortion and compression of the aqueduct, with destruction of part of the left pulvinar and part of the mesencephalon.

Comment.—The extension of the tumor into the caudal part of the left hypothalamus undoubtedly resulted in lethargy. The role played by other involved hypothalamic areas and the compression of the thalamus and basal ganglia in sleep dysfunction cannot be ruled out.

CASE 7.—*Meningioma at the base of the brain; compression of and hemorrhages into the hypothalamus. Insomnia followed by somnolence. Increased intracranial pressure.*

G. M., a man aged 44, had complained of insomnia, vertigo, diminished vision and olfactory hallucinations for four years.

Neurologic Examination.—Examination revealed bilateral anosmia, irregular pupils, poor ocular convergence and generalized hyporeflexia. One week after admission the patient became drowsy and dull. On being aroused, he was able to concentrate for only a short time before relapsing into sleep. At times there were periods of hyperactivity, alternating with sleepiness. At operation a large meningioma was removed from the base of the brain. The patient died the same day.

Laboratory Data.—The cerebrospinal fluid showed an initial pressure of 280 mm. of water and 108 mg. of protein per hundred cubic centimeters. The urine and blood were normal. The nonprotein nitrogen of the blood measured 31 mg. per hundred cubic centimeters.

Autopsy.—There was a large excavation in the orbital surface of the right frontal lobe from removal of the tumor. Small hemorrhages, with decomposition of red cells, were found in the internal capsule, the striatum and the posterior hypothalamic nuclei on the right side. There were numerous avascular areas in which the nerve and glia cells of the hypothalamus had disappeared, while other nerve cells disclosed extensive changes, disintegration, chromatolysis and disappearance of Nissl substance.

Comment.—The sleepiness in this case must have resulted from the hemorrhages in the posterior part of the hypothalamus. These hemorrhages were present prior to the operation, as they showed evidence of decomposition of red cells. The insomnia which preceded the somnolence may have been caused by compression of the anterior part of the hypothalamus. The involvement of the basal ganglia and their influence on disturbance of sleep cannot be ruled out.

CASE 8.—*Adenoma of the pituitary gland with compression and invasion of the hypothalamus. Insomnia later replaced by short periods of drowsiness. Increased intracranial pressure.*

L. G., a boy aged 8 years, had daily attacks of projectile vomiting, restlessness and insomnia. A month later he experienced frontal headaches, dizziness, poor vision and attacks of drowsiness, lasting one to several minutes, during which time he would appear as though in a trance. He could always be aroused.

Neurologic Examination.—Examination disclosed bilateral papilledema; atrophy of the optic nerves, irregularity of the pupils, with sluggish reaction to light; areflexia; a bilateral Babinski sign, and nuchal rigidity. Studies of the spinal fluid were not recorded.

Autopsy.—An adenoma of the pituitary projected into the circle of Willis, compressing all its vessels, the optic nerves, chiasm and tracts, the third and sixth nerves and the floor of the third ventricle (figure 7). Part of the neoplasm actually invaded the hypothalamus. The nerve cells of the various hypothalamic nuclei, especially in the infundibular region, showed all types of pathologic changes, such as disintegration, chromatolysis, loss of iron pigment or a shadow-like appearance. The thalamus and the basal ganglia were normal.

Comment.—This case was of interest because the patient at first suffered from insomnia and later from short periods of drowsiness almost resembling narcolepsy. There were invasion and compression of the entire hypothalamus.

CASE 9.—*Adenoma of the pituitary gland with compression of and pathologic changes in the hypothalamic nerve cells. Somnolence. Increased intracranial pressure.*

L. O., a woman aged 50, complained of drowsiness and fatigue in the early evening.

Neurologic Examination.—Examination revealed mental hebetude, hypertension, hyperglycemia and primary atrophy of the optic nerve bilaterally. The left pupil reacted to light but not in accommodation. There was paralysis of the left sixth nerve.

Laboratory Data.—The blood urea nitrogen varied from 22 to 40 mg., and the blood sugar at times was increased to 220 mg. per hundred cubic centimeters. The cerebrospinal fluid was not studied.

Autopsy.—A large tumor of the pituitary gland between the two cerebral peduncles compressed the floor

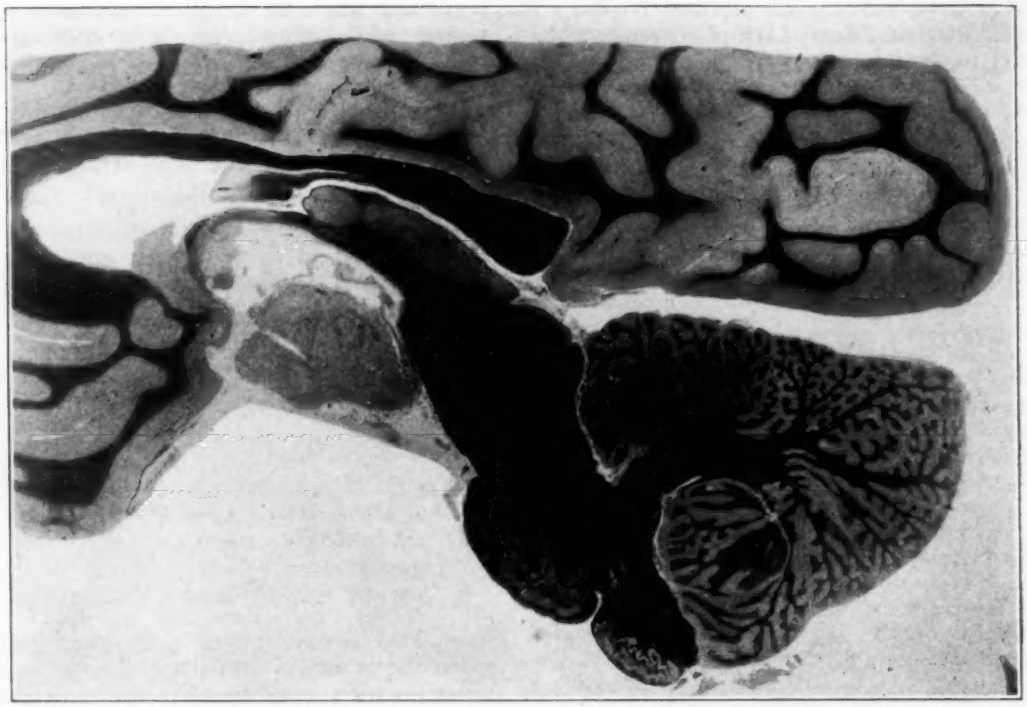

Fig. 7 (case 8).—Adenoma of the pituitary gland, with invasion and compression of the hypothalamus.

Fig. 8 (case 10).—Glioblastoma multiforme of the right hypothalamus and the right side of the diencephalon. Note the compression of the opposite hypothalamus.

of the third ventricle and the hypothalamus. The various hypothalamic nerve cells, both anteriorly and posteriorly, showed pathologic changes, such as loss in Nissl substance, shrinkage, pyknosis and loss of iron pigment. The thalamus and the basal ganglia were normal.

CASE 10.—*Glioblastoma multiforme of the right diencephalon, with unilateral invasion of the hypothalamus but with bilateral pathologic changes, more pronounced on the right side. Drowsiness; stupor. Increased intracranial pressure.*

S. L., a man aged 60, became drowsy and dozed off frequently for short periods during the day. He became careless about his appearance and lost interest in his surroundings.

Neurologic Examination.—The patient was stuporous. He responded with grimaces to painful stimuli and could be awakened with difficulty. There were bilateral papilledema, conjugate deviation of the eyes to the right, mimetic palsy of the left side of the face, hyporeflexia, tremors and coarse involuntary movements of the upper extremities. Studies of the spinal fluid were not recorded.

Autopsy.—A large tumor destroyed the following structures on the right side: the inferior part of the internal capsule, the thalamic nuclei and the middle and caudal portions of the hypothalamus. The right striatum and pallidum and the left hypothalamus were compressed (fig. 8). The remaining hypothalamic nerve cells on the right side were either completely destroyed or showed marked pathologic change. The nerve cells of the left hypothalamus showed loss of Nissl substance and heavy granules of iron pigment.

Comment.—Drowsiness in this case could be explained on the basis of involvement of the caudal part of the hypothalamus. The thalamohypothalamic and striohypothalamic pathways may also have played a role in this dysfunction.

CASE 11.—*Glioblastoma multiforme of the left temporal lobe with metastases to the hypothalamus, involving essentially the infundibular and mamillary regions. Hypothermia, ocular manifestations and somnolence. Increased intracranial pressure.*

Fig. 9 (case 11).—Glioblastoma multiforme with metastases to the hypothalamus, involving essentially the infundibular and mamillary regions (*A*, myelin sheath stain; *B*, cresyl violet stain).

S. A., a man aged 31, had a glioblastoma multiforme in the left temporofrontal region; the tumor has been partially removed. After a second operation hyperthermia developed. Five months later the patient began to have projectile vomiting, headaches and drowsiness, from which he could be aroused. At this time there was marked hypothermia. The right pupil did not respond to light or in accommodation, and there was weakness of the left lateral rectus muscle.

Laboratory Data.—The blood chemistry was normal. The spinal fluid was clear, contained 75 mg. of protein per hundred cubic centimeters and showed an initial pressure of 200 mm. of water.

Autopsy.—The third frontal and the temporal convolutions on the left side were the seat of a neoplasm. The tumor invaded the rostral, middle and caudal hypo-

thalamic nuclei (fig. 9). The greatest involvement was in the medial wall of the middle and caudal portions of the hypothalamus. Most of the nerve cells of the supraoptic and lateral hypothalamic areas were well preserved. There were compression and edema of the thalamus and the basal ganglia on the right side.

Comment.—The patient's drowsiness during the past month and the hypothermia were undoubtedly caused by the neoplastic invasion of the caudal part of the lateral hypothalamic areas, where the destructive process seemed most advanced. The lethargy in this instance did not appear until the tumor invaded the hypothalamus. The involvement of the thalamus and the basal ganglia may also have played a role in the somnolence.

CASE 12.—*Glioblastoma multiforme involving the posterior part of the hypothalamus, pulvinar and mesencephalon. Insomnia, followed by somnolence. No evidence of increased intracranial pressure.*

T. I., a man aged 58, first experienced insomnia and later somnolence, from which he could be aroused.

Neurologic Examination.—There were a left hemisensory syndrome and bilaterally diminished hearing.

Laboratory Data.—The blood chemistry was normal. The spinal fluid was clear and contained 1 cell per cubic millimeter and 62 mg. of protein per hundred cubic centimeters; the initial pressure was 144 mm. of water.

Autopsy.—There was a tumor in the region of the pulvinar, the thalamic nuclei and the hypothalamus on the right side, with compression of the posterior part of the opposite side of the hypothalamus and the mesencephalon. Other discrete masses on the right side were present in the thalamic nuclei, the peduncle close to the external geniculate body and the white matter near the temporal lobe and the island of Reil. Some of the fibers of the internal capsule were involved. In sections through the pons, the tumor involved the nuclei of the third and fourth cranial nerves and the posterior longitudinal bundle. The nerve cells of the posterior part of the hypothalamus showed all types of pathologic changes, such as diminution, shrinkage, chromatolysis and complete destruction.

Comment.—The tumor in this instance was essentially situated in the caudal hypothalamic region and the thalamus and mesencephalon. Clinically, there was no evidence of involvement of the ocular nerves; pathologically, however, the third and fourth nerve nuclei and the posterior longitudinal bundle were implicated. The role played by the thalamus in sleep dysfunction cannot be totally ruled out in this case.

CASE 13.—*Hemorrhage in the diencephalon and mesencephalon. Somnolence. Clinical evidence of increased intracranial tension.*

H. I., a man aged 64, after an emotional upset had an attack of dizziness, blurred vision and diplopia.

Neurologic Examination.—Examination disclosed signs of involvement of the pyramidal tract and pathologic reflexes on the left, a right hemisensory syndrome and nystagmus on lateral gaze. Later the patient became somnolent but could be aroused.

Laboratory Data.—The blood chemistry was normal. Studies of the spinal fluid showed no cells, a negative Pandy reaction, 39 mg. of protein per hundred cubic centimeters and an initial pressure of 80 mm. of water.

Autopsy.—A massive hemorrhage on the right side had destroyed the external capsule, the claustrum, the putamen, part of the internal capsule and part of the thalamic and the middle and caudal hypothalamic nuclei (fig. 10). The hemorrhage extended into the rostral part of the mesencephalon. The nerve cells of the hypothalamic nuclei had a washed-out appearance, with evidence of chromatolysis, ischemia and conspicuous loss of iron pigment.

Comment.—The somnolence which appeared toward the end of the illness was due to extensive hemorrhages in the diencephalon and the rostral part of the mesencephalon. The influence of the thalamus and the basal ganglia on this dysfunction cannot be ruled out.

CASE 14.—*Encephalitis lethargica. Lesions of the basal ganglia and hypothalamus. Reversal of sleep mechanism—somnolence during the day and insomnia at night. Ocular manifestations. No increased intracranial pressure.*

O. E., a woman aged 20, gave a history of influenza in 1920 and symptoms of asthenia, dizziness, diplopia, drowsiness with excessive sleepiness during the daytime, from which she could be aroused, and insomnia during the night. Later, a typical picture of paralysis agitans developed. There were periods of amenorrhea during her illness.

Neurologic Examination.—There was a typical picture of paralysis agitans, the right pupil was greater than the left, and both reacted sluggishly to light. There was some disturbance in convergence.

Laboratory Data.—The blood chemistry was normal. The spinal fluid was clear and contained no cells. The total protein measured 24 mg. per hundred cubic centimeters. The pressure was stated to be normal.

Autopsy.—The pathologic picture of the pallidum and substantia nigra was typical of paralysis agitans, with areas of necrobiosis and calcification of vessels. There was also a small area of necrobiosis in the right nucleus supraopticus. The ganglion cells of the caudal hypothalamic nuclei stained poorly and did not have the high content of iron generally seen.

Comment.—The lethargy in this case was most likely the result of the lesions in the striohypothalamic pathways and the hypothalamus. The role played by the basal ganglia cannot be ruled out.

CASE 15.—*Paralysis agitans. Lesions in the basal ganglia and, to a lesser extent, in the hypothalamus. Ocular manifestations; somnolence. No increased intracranial pressure.*

S. M., a woman aged 42, had diplopia, drowsiness and then somnolence, lasting five months, from which she could be awakened. Lumbar punctures, performed every three months, relieved the hypersomnia for short periods.

Neurologic Examination.—Examination disclosed a typical picture of paralysis agitans. The pupils reacted to light, but there was paralysis of accommodation and convergence. The temperature was often 97 F., and terminally it reached 96 F.

Laboratory Data.—The blood chemistry was normal. Spinal puncture disclosed a clear fluid, with no cells

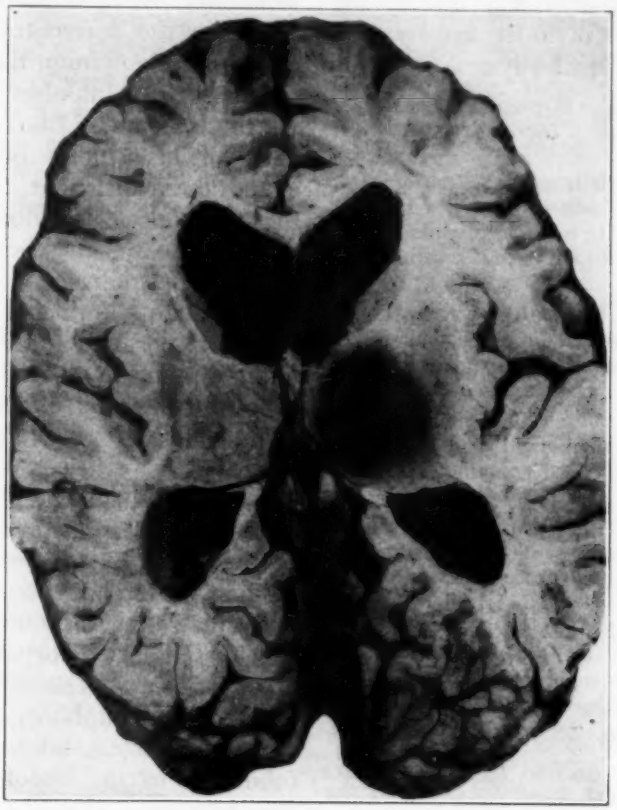

Fig. 10 (case 13).—Hemorrhages in the hypothalamus and thalamus.

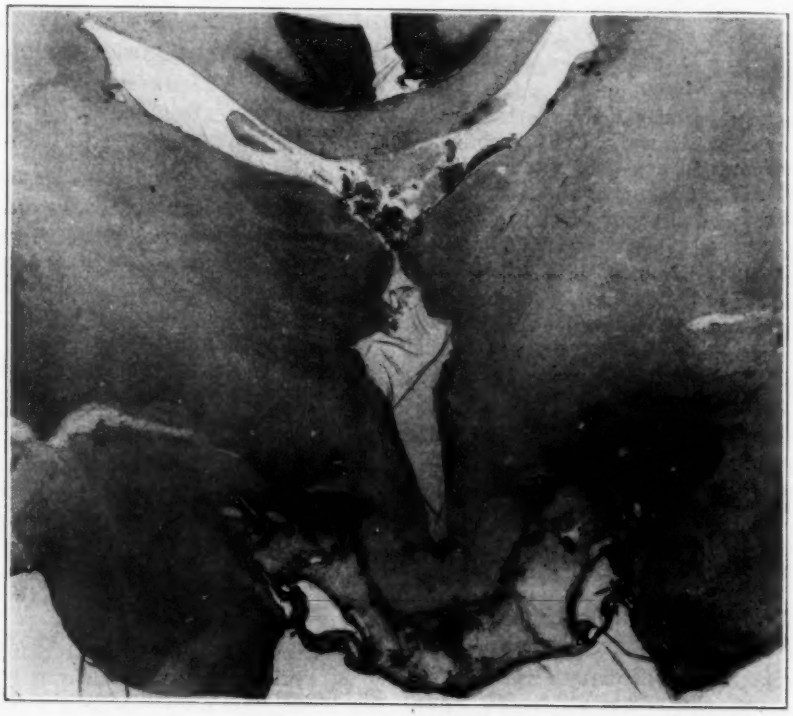

Fig. 11 (case 16).—Tuberculous basilar meningitis, invading the hypothalamus.

and a total protein content of 19 mg. per hundred cubic centimeters. Pressure readings were not recorded.

Autopsy.—The basal ganglia showed the changes typical of paralysis agitans, with extensive involvement of the pallidum and the substantia nigra. The hypothalamic nerve cells, especially those of the caudal part, were diminished in number and shrunken and showed lack of pigment granules.

Comment.—Although this case was placed in the diencephalic group, it is difficult to state with

certainty whether the lethargy was due to the lesion in the hypothalamus or to the involvement of the striohypothalamic pathways.

CASE 16.—*Tuberculous basilar meningitis; invasion of the hypothalamus. Somnolence. Increased intracranial pressure.*

D. L. P., a man aged 36, left home in search of work and was found several days later in another city. He complained of being sleepy. He fell asleep while talking and remained in continuous stupor except when strong stimuli were applied.

Neurologic Examination.—The patient was apathetic, disoriented, especially spatially, and somnolent. The temperature was 104 F. Kernig and Brudzinski signs were elicited, and pyramidal tract signs were present bilaterally.

Laboratory Data.—The spinal fluid had an initial pressure of 280 mm. of water and contained 270 cells per cubic millimeter.

Autopsy.—The meninges at the base were extensively thickened and showed evidence of tuberculous meningitis. Part of the inflammatory process extended into the region of the hypothalamus (fig. 11). The various hypothalamic nuclei, especially those in the inferior and caudal parts, disclosed all types of pathologic changes, such as neuronophagia, severe cell changes of Nissl, complete disintegration and loss of pigment granules. The thalamus and the basal ganglia were normal.

CASE 17.—*Torular meningitis, involving especially the base of the brain, with invasion of the hypothalamic nuclei and other diencephalic structures. Insomnia, followed by somnolence. Increased intracranial pressure.*

U. M., a man aged 63, gave a history of falling while walking. He also became lethargic and had a tremor of the upper extremities. Two years prior to this illness he had suffered from insomnia.

Neurologic Examination.—The patient was lethargic, with an attitude of indifference and lack of emotional display. Intention tremor and cogwheel rigidity were present bilaterally. Toward the end of his illness the patient had a decerebrate fit, became deeply stuporous and could not be aroused.

Laboratory Data.—All laboratory tests, including studies of the blood chemistry, gave normal results. The spinal fluid was clear and contained no cells; the Pandy reaction was strongly positive; the total protein was 47 mg. per hundred cubic centimeters, and the initial pressure was 140 mm. of water.

Autopsy.—Extensive torular meningitis involved the optic nerves, chiasm and tracts, the floor of the third ventricle, the basal ganglia, the hypothalamic nuclei and the peduncles. The nerve cells of the various hypothalamic nuclei showed all types of pathologic changes. There was internal hydrocephalus.

Comment.—The somnolence was most likely the result of implication of the hypothalamus and the striohypothalamic pathways. This case is of further interest because of the initial period of insomnia, followed by somnolence in two years.

GENERAL COMMENT

Lesions of the diencephalon, especially in the hypothalamic region, are well known to be the most frequent cause of disturbances of sleep. Mauthner,[3] in 1890, postulated a sleep-regulating center in the periventricular gray matter. He expressed the opinion that this center influenced the passage of impulses to and from the cortex via the thalamus. Later, von Economo,[4] on the basis of his studies on lethargic encephalitis, stated the belief that this center extended in the anteroposterior direction from the hypothalamus to the mesencephalon and laterally to the basal ganglia. He expressed the opinion that inhibitory influences pass from this region to the cerebrum, on the one hand, and to the midbrain, on the other. He postulated a specific center for insomnia and another for hypersomnia. The center for insomnia, or wakefulness, he located in the anterior part of the hypothalamus, close to the basal ganglia, while the center for hypersomnia, somnolence or lethargy he located in the posterior part of the hypothalamus, extending as far back as the aqueduct of Sylvius and implicating the nuclei of the ocular nerves. He distinguished between "brain sleep" and "body sleep." The former, he asserted, was the result of inhibitory influences on the thalamus and cortex, while the latter was due to inhibition of the hypothalamic centers. Many investigators (Pötzl,[5] Lesniowski,[6] Jacarelli,[7] Tsutsui,[8] Pette[9] and others) accepted this point of view. Pötzl,[5] however, attempted to place the center more posteriorly, in the region of the nuclei of the posterior longitudinal bundle, while Pette[9] expressed the belief that there is a close connection between these centers and the endocrine system. Skliar[10] stated that the periventricular gray matter acts as an inhibitory center on the cerebral cortex, while Retif[11] asserted that there is a reciprocal inhibition between the mesencephalic centers and the cere-

3. Mauthner, L.: Zur Pathologie und Physiologie des Schlafes, Wien. klin. Wchnschr. **40**:961, 1001, 1049, 1092, 1144 and 1185, 1890.

4. von Economo, C.: Ueber den Schlaf, Wien. klin. Wchnschr. (supp.) **38**:1, 1925; Studien über den Schlaf, ibid. **76**:91, 1926; Schlaftheorie, Ergebn. d. Physiol. **28**:312, 1929.

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7. Jacarelli, E.: I disturbi del sonno nelle lesioni del mesencefalo, Policlinico (sez. med.) **39**:452, 1932.

8. Tsutsui, H.: Ein Beitrag zur Pathophysiologie des Mittel- und Zwischenhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **157**:717, 1937.

9. Pette, H.: Zur Anatomie und Pathologie der Schlafregulations Zentrum, Zentralbl. f. d. ges. Neurol. u. Psychiat. **51**:234, 1928-1929.

10. Skliar, N.: Ueber die Entstehung des Schlafes, J. nevropat. psikhiat. **21**:621, 1920.

11. Retif, E.: Le sommeil dissocié; auto-observation, Rev. neurol. **1**:880, 1927.

bral cortex. Marinesco, Sager and Kreindler [12] and others stated the opinion that sleep is not controlled by a single center but is the result of action of a system of centers, in which the endocrine component acts as a sensitizer of the vegetative centers. They also concluded that sleep is a combination of conditioned and unconditioned reflexes. Adie,[13] on the basis of evidence derived from cases of narcolepsy, favored an endocrine-neural mechanism located in the floor of the diencephalon, in and around the vegetative centers forming the hypophysial-diencephalic system.

Other authors, while of the opinion that the diencephalon acts as a sleep center, stated the belief that the thalamus is the important regulating center (Inaba,[14] Trömner,[15] Hirsch,[16] Lucksch,[17] Brailovsky,[18] Salmon,[19] Spiegel [20] and others). Trömner stated that the thalamus is the only structure to inhibit cortical centers and to regulate the action of the intrinsic and extrinsic ocular muscles and other functions attributed to the hypothalamus. He asserted that the thalamus influences hypothalamic centers and that disturbances in sleep can be produced only by bilateral lesions in the thalamus. Ranson [21] failed to produce somnolence in several monkeys with extensive bilateral lesions of the thalamus. Harrison [22] induced somnolence with passage of a destructive current through the thalamus in cats but was not certain that this action was due to the thalamus alone. Stimulation of the thalamus, however, by Mussen [23]; Kabat, Anson, Magoun and Ranson,[24] and Harrison,[22] did not result in disturbances in sleep.

There are numerous clinicopathologic contributions describing disturbances of sleep as a result of lesions in the diencephalic region (Fulton and Bailey,[25] Lucksch,[17] Hirsch,[16] Strauss and Globus,[26] Lhermitte and Tournay,[27] Adie,[13] Adler,[28] Rowe,[29] Cox,[30] Engel and Aring [31] and others). In some of the cases previously reported, as in some of ours, the lesions were widespread and frequently associated with compression or edema of adjacent areas.

The oculomotor phenomena observed in cases of encephalitis in connection with somnolence have been emphasized by some observers as an indication that the sleep center is situated in the vicinity of the aqueduct, the seat of most of the nuclei of the oculomotor nerves (Frank,[32] von Stockert,[33] Kahn [34] and others). Postulation of localization on this basis alone must be accepted with reservation. The ocular manifestations in cases with neoplasms are undoubtedly secondary effects resulting from compres-

12. Marinesco, G.; Sager, O., and Kreindler, A.: Recherches expérimentales sur le mécanisme du sommeil, Bull. Acad. de méd., Paris **100**:752, 1928.

13. Adie, W. J.: Idiopathic Narcolepsy: A Disease Sui Generis; with Remarks on the Mechanism of Sleep, Brain **49**:257, 1926.

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16. Hirsch, E.: Zur Frage der Schlafzentren im Zwischenhirn des Menschen, Med. Klin. **20**:1322, 1924.

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18. Brailovsky, V.: Ueber die pathologische Schläfrigkeit und das Schlafzentrum, Ztschr. f. d. ges. Neurol. u. Psychiat. **100**:272, 1926.

19. Salmon, A.: Le rôle des corrélations cortico-diencéphaliques et diencéphalo-hypophysaires dans la régulation de la veille et du sommeil, Presse méd. **45**: 509, 1937.

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21. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1 (Jan.) 1939.

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24. Kabat, H.; Anson, B. J.; Magoun, H. W., and Ranson, S. W.: Stimulation of the Hypothalamus with Special Reference to Its Effect on Gastro-Intestinal Motility, Am. J. Physiol. **112**:214, 1935.

25. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1, 145 and 261, 1929.

26. Strauss, I., and Globus, J. H.: Tumor of the Brain with Disturbance in Temperature Regulation, Arch. Neurol. & Psychiat. **25**:506 (March) 1931.

27. Lhermitte, J., and Tournay, A.: Rapport sur le sommeil normal et pathologique, Rev. neurol. **1**:751, 1927.

28. Adler, E.: Zur Lokalisation des "Schlafzentrums," Med. Klin. **20**:1321, 1924.

29. Rowe, S. N.: Localization of the Mechanism Controlling Sleep, Arch. Neurol. & Psychiat. **33**:440 (Feb.) 1935.

30. Cox, L. B.: Tumors of the Base of the Brain: Their Relation to Pathological Sleep and Other Changes in the Conscious State, M. J. Australia **1**:742, 1937.

31. Engel, G. L., and Aring, C. D.: Hypothalamic Attacks with Thalamic Lesion, Arch. Neurol. & Psychiat. **54**:1 (July) 1945.

32. Frank, C.: Intorno alla mia scoperta di due nuclei de mesencefalo dell'uomo ed ulteriori studi sui nuclei oculomotri dei mammiferi, Arch. gen. di neurol., psichiat. e psicoanal. **11**:1, 1940.

33. von Stockert, F. G.: Die Beziehungen der Augenmuskeln zum Schlaf, Med. Klin. **29**:697, 1933.

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sion or edema of the tegmentum adjacent to the hypothalamus.

In addition to the clinical evidence that the hypothalamus is concerned with the regulation of sleep there are experimental physiologic (lesions and stimulation) and pharmacologic data to substantiate this theory. A review of this material will be given in a subsequent publication.

On the basis of observation derived from this and from other series of cases, as well as evidence of a neuroanatomic and neurophysiologic character, the following afferent and efferent connections concerned with the sleep mechanism can be postulated.

Thalamohypothalamic and Hypothalamothalamic Pathways.—The evidence of the existence of such pathways seems to be accepted by all investigators. Whether these are afferent or efferent has not been determined. They consist of fibers which arise from the medial and midline thalamic nuclei and go to the hypothalamic nuclei. There may be connections via the inferior thalamic peduncle with the rostral hypothalamic and the lateral tuberal nuclei. Many fibers from the substantia innominata enter the lateral preoptic and hypothalamic areas dorsal to the supraoptic nucleus.

Thalamomamillary Fibers.—These fibers set up relays of somatic, visceral and sensory impulses from the neopallium to the hypothalamus. The impulses from the hypothalamus to the thalamus are mediated via the mamillothalamic tract. The mamillothalamic tract most likely serves as a link between the hypothalamus and the cerebral cortex, especially the gyrus cingulus. The mamillotegmental tract arises in the mamillary bodies and descends through the central gray matter of the aqueduct, with possible contributions to the tectal and tegmental nuclei.

Stria Terminalis.—This pathway, which also contains preoptic and hypothalamic components, conveys fibers from the amygdaloid nucleus to the hypothalamus.

Supraoptic Commissures. — According to Papez [35] and others, these structures are afferent systems concerned with the integration of emotional expressions.

Striopallido Hypothalamic and Subthalamohypothalamic Connections.—Such connections have been reported by many observers, but the evidence is not entirely conclusive.

Hypothalamohypophysial Pathway.—This well known tract runs from the supraoptic, paraventricular and tuberal nuclei to the neurohypophysis.

Intrahypothalamic Pathways.—These tracts form connections between the various hypothalamic nuclei.

Résumé.—Our series includes 17 cases with diencephalic lesions. In 8 cases there was a neoplasm of the hypothalamus, in 2 of which the lesion was metastatic. In 2 cases a pituitary tumor and in 2 a suprasellar tumor either compressed or invaded the hypothalamus. The other cases of lesions of the hypothalamus included 2 of basilar meningitis (1 of torular meningitis), 2 of paralysis agitans following lethargic encephalitis and 1 of hemorrhage within the hypothalamus. In 14 of the 17 cases intrahypothalamic lesions were disclosed. In 16 cases the caudal part of the lateral hypothalamic area showed changes bilaterally. There were only 7 cases of pure hypothalamic lesions, without involvement of the thalamic or basal ganglia (cases 1, 2, 3, 4, 8, 9 and 16). A correlation between insomnia or somnolence and involvement of specific parts of the hypothalamus could not be definitely established from our series because the caudal portion of the hypothalamus was solely affected only in 1 instance (case 3). Although the caudal part of the hypothalamus was involved in most of the other cases (1, 2, 3, 8, 9 and 16), the anterior and middle parts were also affected. This problem becomes even more complicated in the remaining cases, in which there was additional implication of the thalamus and the basal ganglia. Besides the hypothalamic involvement, there was implication of the thalamus in 2 cases (11 and 12), of the thalamus and basal ganglia in 4 cases (3, 5, 6 and 13) and of the basal ganglia in 4 cases (7, 10, 14 and 17). A reversal of the sleep mechanism was present in 2 cases, while in 4 others (1, 8, 12 and 17) the insomnia was followed by somnolence. In these cases both the rostral and the caudal portion of the hypothalamus were diseased. It is probable that in some of the cases with insomnia the rostral part of the hypothalamus became affected first. Somnolence appeared when the lesion extended into the caudal portion of the hypothalamus. Evidence of increased intracranial pressure was present in 13 cases. This high incidence of increased intracranial pressure is to be expected in this group, since the third ventricle was obstructed, especially in the cases with neoplasms. In 1 case there was no clinical evidence of this phenomenon, but internal hydrocephalus was observed at autopsy. In 4 cases (6, 12, 14 and 15) there was no evidence of increased intracranial pressure.

35. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725 (Oct.) 1937.

These were 2 cases of paralysis agitans, a case of suprasellar meningioma and a case of glioblastoma multiforme. Ocular manifestations, consisting of diplopia, ptosis, defective convergence, paralysis or paresis of the ocular muscles and nystagmus, were present in 14 cases; in 1 case ocular disturbances were not recorded. The ocular manifestations were undoubtedly the result of compression or edema of the tegmentum. These disturbances were more prevalent in this group than in the cases of cortical or corticodiencephalic lesions because of the proximity of the ocular nerve nuclei to the posterior part of the hypothalamus. Endocrine disturbances, such as changes in metabolism, adiposity, adiposogenital dystrophy, early menopause and loss of libido, were present in 4 cases (1, 2, 3 and 14). Deviations in temperature from the normal were present in 9 cases; hypothermia was present in 5 cases and hyperthermia in 4 cases. In 1 case hyperthermia was later followed by hypothermia. Disturbances in temperature should be expected in this group, as the hypothalamic nuclei are concerned with this mechanism.

SUMMARY AND CONCLUSIONS

Of 17 cases of pathologic sleep, there was direct involvement of the hypothalamus in 14 cases. In 3 cases there was compression of the hypothalamus with pathologic changes in its nerve cells. In 16 cases the caudal part of the lateral hypothalamic area showed changes bilaterally. There were, however, only 7 cases with pure hypothalamic involvement. In the remaining 10 cases there was also invasion, compression or edema of either the thalamus or the basal ganglia or of both, with implication of the thalamohypothalamic and striohypothalamic pathways.

Increased intracranial pressure was present in 13 cases and absent in 4. A high incidence of increased intracranial pressure in this series should be expected, as the neoplasm encroached on the ventricular system.

Ocular manifestations, in the form of diplopia, ptosis, defective conjugate deviation, paralysis or paresis of ocular muscles, or nystagmus, were present in 14 cases. These symptoms were undoubtedly the result of compression or edema of the nuclei of the ocular nerve or their pathways.

Endocrine disturbances were present in 4 cases. In all these cases the tumor was situated in the pituitary region or there was compression of the hypophysial duct or gland.

Deviations in temperature were present in the form of hypothermia in 5 cases and of hyperthermia in 4 cases.

From this series of cases of diencephalic lesions, it may be concluded that damage to the hypothalamus, especially the posterior part of the lateral hypothalamic area and of its various pathways bilaterally, causes somnolence. The influence of the thalamus or the basal ganglia on this disturbance cannot be completely ruled out.

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DISTURBANCES IN SLEEP MECHANISM: A CLINICOPATHOLOGIC STUDY

IV. LESIONS AT THE MESENCEPHALOMETENCEPHALIC LEVEL

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Disturbances in sleep mechanism as a result of lesions of the pons and medulla oblongata, although rare, have been reported by a number of observers. Some investigators are of the opinion that somnolence in cases of such lesions is caused by involvement of the nuclei of the ocular nerves, which are situated in the mesencephalon and metencephalon. They believe that the sleep-regulating center is located in the region of these cranial nerve nuclei and that there is a connection between sleep and the ocular mechanism.

In our group of 8 cases, it was possible to demonstrate that the descending hypothalamic pathways in the brain stem were invariably implicated. Somnolence in these cases was probably due to the lesions in these pathways. Involvement of the nuclei of the ocular nerves was secondary to the specific location of the lesion in the brain stem and most likely played an insignificant role in the disturbance in sleep mechanism.

REPORT OF CASES

CASE 1.—*Hemangioblastoma of the cerebellum; changes in the medulla oblongata, including the nerve cells of the vegetative nervous system. Nystagmus; periodic lethargic episodes. Pathologic evidence of increased intracranial pressure.*

C. C., a man aged 36, had spells of sleepiness and weakness at the age of 12 years. Later, he remembered his head falling forward while he was tuning a piano, followed by a dreamless sleep lasting five to fifteen minutes. At the age of 24, the periods of somnolence recurred, and he would have to go to bed because of weakness. He had been drowsy and easily fatigued ever since, although he could always be aroused. The right eye had been enucleated after a trauma twenty years ago; vision in the left eye progressively diminished and was completely lost thirteen years ago, as a result of Lindau's disease. Other symptoms, not mentioned in this presentation, had no bearing on the problem under discussion.

Neurologic Examination.—Examination revealed bilateral cerebellar signs, nystagmus in all directions, muscular weakness, blindness of the left eye and numerous hemangiomas of the skin.

Laboratory Data.—There was moderate polycythemia. A spinal tap was stated to show normal fluid, without increase in manometric pressure. The blood chemistry was normal. The temperature throughout the course of the illness was normal.

Autopsy.—There was uniform internal hydrocephalus. The fourth ventricle was filled with a hemangioblastoma, which did not invade any of the cerebellar structures (fig. 1). The medulla oblongata, the pons and part of the vermis cerebelli were compressed by the tumor. The various nerve cells of the nuclei within the medulla oblongata, including those of the vegetative nervous system, showed all types of pathologic changes, such as shadow-like appearance, disintegration, chromatolysis, shrinkage and pyknosis. The nerve cells of the hypothalamus displayed no abnormality except for occasional loss in pigment granules.

Comment.—In this instance, the tumor was essentially situated in the posterior fossa. Although the hypothalamus was not involved, its descending fibers were affected, resulting in somnolence.

CASE 2.—*Hemangioblastoma of the cerebellum with compression of the metencephalon. Ocular manifestations; drowsiness, with inversion of the sleep mechanism. Increased intracranial pressure.*

B. S., a man aged 44, complained that he constantly wanted to sleep. He used to sit down and sleep for half an hour, awakening with a terrific headache. Thereafter he was frequently noted to be drowsy, and he became increasingly irritable. Later there developed an inversion of the sleep mechanism, in that he slept spasmodically during the day and not at all during the night. He could be aroused from his sleep. Unsteadiness of gait, dysphagia, exophthalmos, diplopia and loss of libido developed.

Neurologic Examination.—Examination revealed papilledema, nystagmus, hyperesthesia of the right cornea and involvement of the tenth, eleventh and twelfth cranial nerves on the right side.

Laboratory Data.—The temperature varied between 97 and 98.8 F., and for three days it was down to 96.2 F. Chemical studies of the blood gave normal

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The paper of which this study is part was presented before the Chicago Neurological Society on May 20, 1943 (preliminary report) and before the New York Academy of Medicine, Section of Neurology and Psychiatry, on Feb. 8, 1944. An abstract of the paper with discussion appeared in the January 1945 issue of the ARCHIVES, page 79.

values. The spinal fluid was clear; the reaction for globulin was negative. Manometric readings were not recorded.

Autopsy.—A hemangioblastoma in the right cerebellopontile angle extended from the lower third of the pons to the end of the medulla oblongata. There was uniform dilatation of the entire ventricular system. The medulla oblongata in the region of the eighth nerve was greatly compressed and distorted (fig. 2). The vegetative nerve cells and those of the cranial nerves in the medulla oblongata showed pathologic changes, such as chromatolysis, retrograde degeneration, shrinkage, pyknosis and complete destruction. The hypothalamus was normal.

fissure was larger than the right. There were bilateral horizontal nystagmus with inconstant upward nystagmus; slight weakness of the internal rectus muscles and frequent yawning and hiccuping. The patient was consistently sleepy. Once the somnolence became profound and was successfully combated with a hypertonic solution of sugar. The temperature was often 97 F. Four months before death he became comatose and was never aroused thereafter.

Laboratory Data.—The spinal fluid contained 4 cells per cubic millimeter; the Pandy reaction was positive; the protein measured 139 mg. per hundred cubic centimeters; the initial pressure was 240 mm. of water. The blood chemistry was normal.

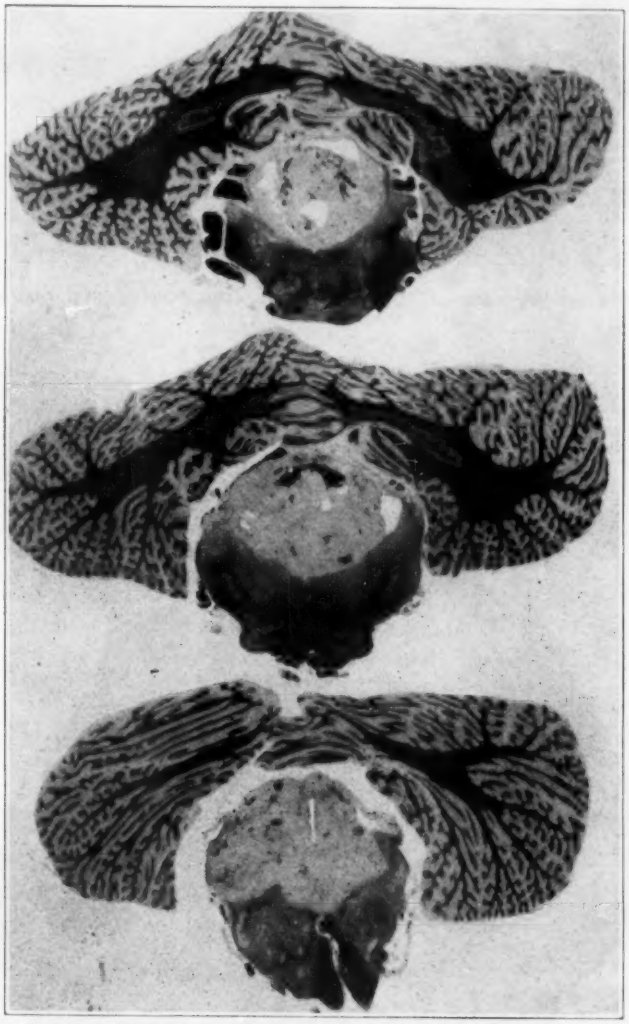

Fig. 1 (case 1).—Hemangioblastoma of the cerebellum, compressing the brain stem.

CASE 3.—*Hemangioblastoma of cerebellum compressing the medulla oblongata. Ocular manifestations; drowsiness, followed later by coma. Increased intracranial pressure.*

A. O., a man aged 33, complained of severe frontal headaches, vomiting, diminished vision and dizziness. A suboccipital exploration revealed a hemangioblastoma in the region of the fourth ventricle.

Neurologic Examination.—There were marked drowsiness, from which the patient could be awakened, bilateral cerebellar signs, slight elevation of the disks and fulness of the veins. The right pupil was larger than the left, and both reacted well to all stimuli. The left palpebral

Autopsy.—There was a tumor between the cerebellar vermis and the medulla oblongata, obliterating the fourth ventricle and compressing the mesencephalon and the metencephalon. The vegetative nerve cells of the medulla oblongata showed pathologic changes. The hypothalamic nuclei did not show any pathologic changes. There was tremendous dilatation of the entire ventricular system.

CASE 4.—*Medulloblastoma of the brain stem; compression of the mesencephalon. Ocular manifestations; somnolence. Increased intracranial pressure.*

G. A., a girl aged 16, had dizziness, diplopia, weakness of the extremities, perversion of the sense of touch and somnolence, from which she could be aroused.

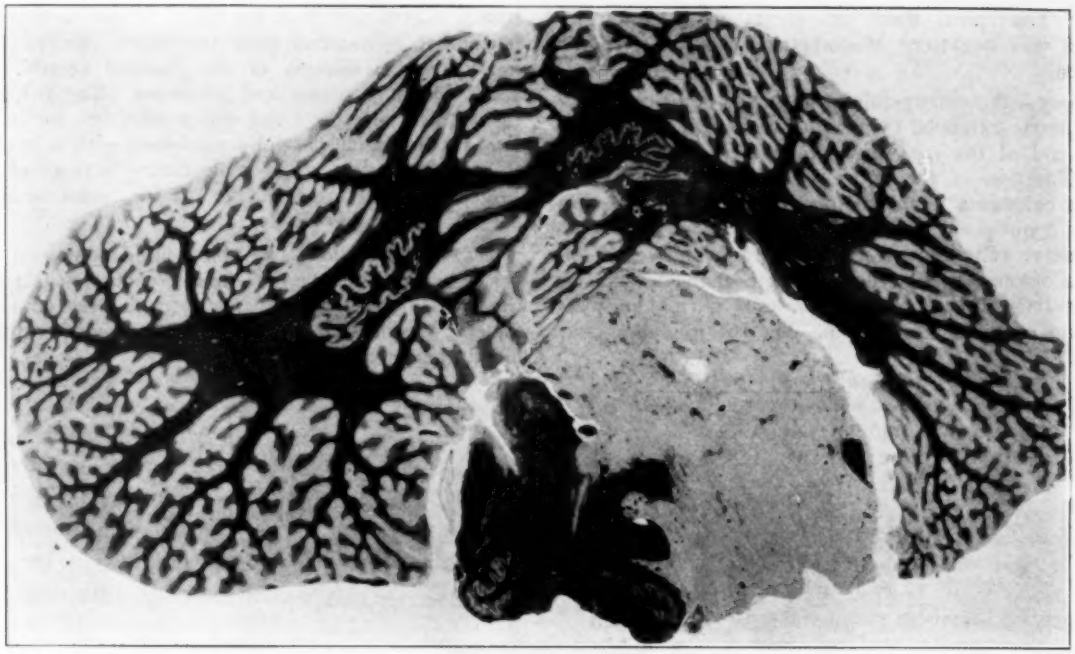

Fig. 2 (case 2).—Hemangioblastoma of the cerebellum, compressing and distorting the brain stem.

Fig. 3 (case 3).—Medulloblastoma of the pons, compressing the mesencephalon, as well as the lower part of the pons.

Neurologic Examination.—Examination disclosed cerebellar signs; bilateral signs of involvement of the pyramidal tract, more marked on the right side; impairment of all forms of sensation on the right side of the body; horizontal and vertical nystagmus; some difficulty in horizontal gaze, and papilledema. The patient later manifested bulbar signs, such as dysphagia and dysarthria. She finally became comatose and could not be aroused.

Laboratory Data.—Chemical studies of the urine and blood gave normal values. The spinal fluid was clear, with an initial pressure of 280 mm. of water, and contained 3 cells per cubic millimeter; the Pandy reaction

was negative, and the total protein was 27 mg. per hundred cubic centimeters.

Autopsy.—There was generalized hydrocephalus. On the left side of the pons was a medulloblastoma, situated mainly in the pyramid and involving the brachium pontis, the medial lemniscus, the rubrospinal tract, the lateral lemniscus, the nuclei of the sixth and seventh nerves, the vestibular nucleus and Deiters' nucleus (fig. 3). The mesencephalon was also compressed. The various vegetative nerve cells showed chromatolysis and occasional shrinkage. The nerve cells of the hypothalamus were normal.

Comment.—Although the tumor was essentially situated in the lower portions of the pons, the mesencephalon was compressed, with involvement of some of the hypothalamic pathways and the sympathetic cells.

initial pressure of 270 mm. of water and a protein content of 147 mg. per hundred cubic centimeters.

Course.—A ventriculogram disclosed symmetric internal hydrocephalus. A suboccipital craniotomy revealed no tumor. After the operation the patient showed marked somnolence, from which he could be aroused. Toward the end the patient became semicomatose but was still able to respond to questioning on stimulation. Just before death he had a high fever.

Autopsy.—There was generalized hydrocephalus. A spongioblastoma polare had destroyed the greater part of the tegmentum, the right side being involved more than the left (fig. 4). The right pyramid was compressed. The following structures were destroyed: the superior and inferior colliculi, the brachium conjunctivum, part of the posterior longitudinal bundle, the lateral and part of the medial lemniscus, the descending hypothalamic tract, the various vegetative nerve cells and the nuclei of the fifth and seventh cranial nerves.

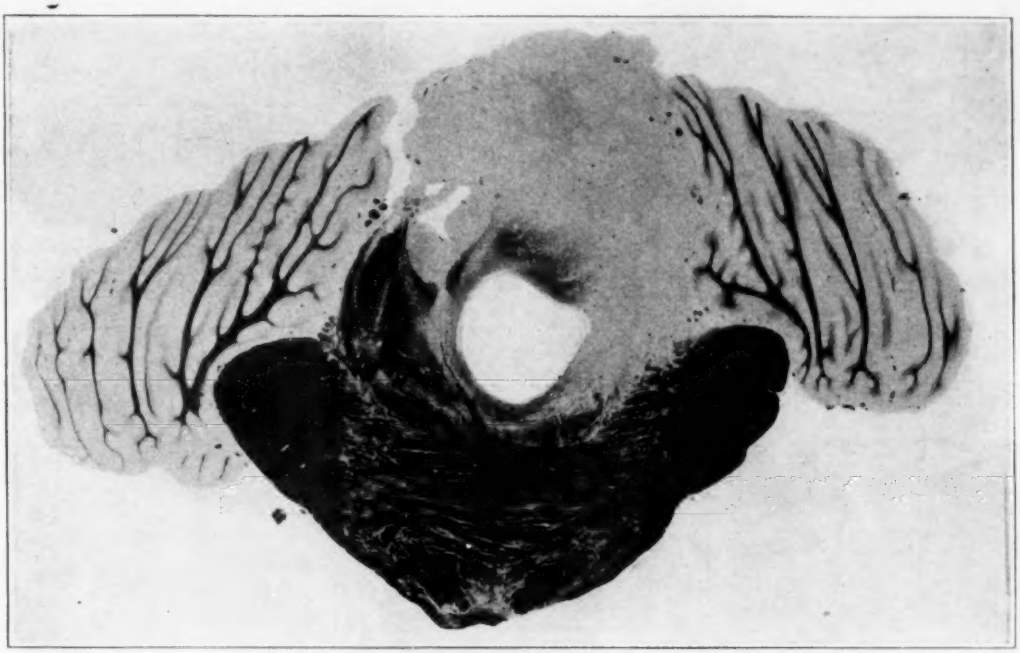

Fig. 4 (case 5).—Spongioblastoma polare, destroying the greater part of the right side of the tegmentum. Myelin sheath stain.

CASE 5.—*Spongioblastoma polare of the mesencephalon. Ocular manifestations; somnolence. Increased intracranial pressure.*

S. P., a man aged 42, had muscular weakness, diplopia, tinnitus, numbness of the left upper extremity, left hemiparesis and staggering gait, with a tendency to fall to the left.

Neurologic Examination.—Examination disclosed bilateral cerebellar signs, more pronounced on the left side; signs of involvement of the left pyramidal tract; disturbances in all modalities over the entire left side of the body; papilledema; absence of the left corneal reflex; bilateral convergent squint and bilateral paresis of the sixth nerve; horizontal and rotary nystagmus on lateral and upward gaze; hypesthesia of the left side of the face; palsy of the left facial nerve of peripheral type, and slight diminution in hearing on the left. The patient was facetious and somewhat depressed and had lack of insight.

Laboratory Data.—Chemical studies of the urine and blood gave normal values. The spinal fluid showed an

There was compression of the nuclei of the other cranial nerves. The nerve cells of the hypothalamus were normal.

Comment.—The somnolence in this case was undoubtedly the result of the partial destruction of the descending hypothalamic pathways and the vegetative nerve cells in the mesencephalon.

CASE 6.—*Glioblastoma multiforme of the brain stem. Ocular manifestations. Lethargy. Clinical evidence of increased intracranial pressure.*

D. L., a boy aged 11 years, complained of dizziness, headache, falling to one side, diplopia and drowsiness, from which he could be awakened.

Neurologic Examination.—Examination revealed a stuporous condition, ataxia and bilateral signs of involvement of the pyramidal tracts, with pathologic reflexes; the right pupil was larger than the left, and weakness of the left fifth and seventh nerves was noted. The

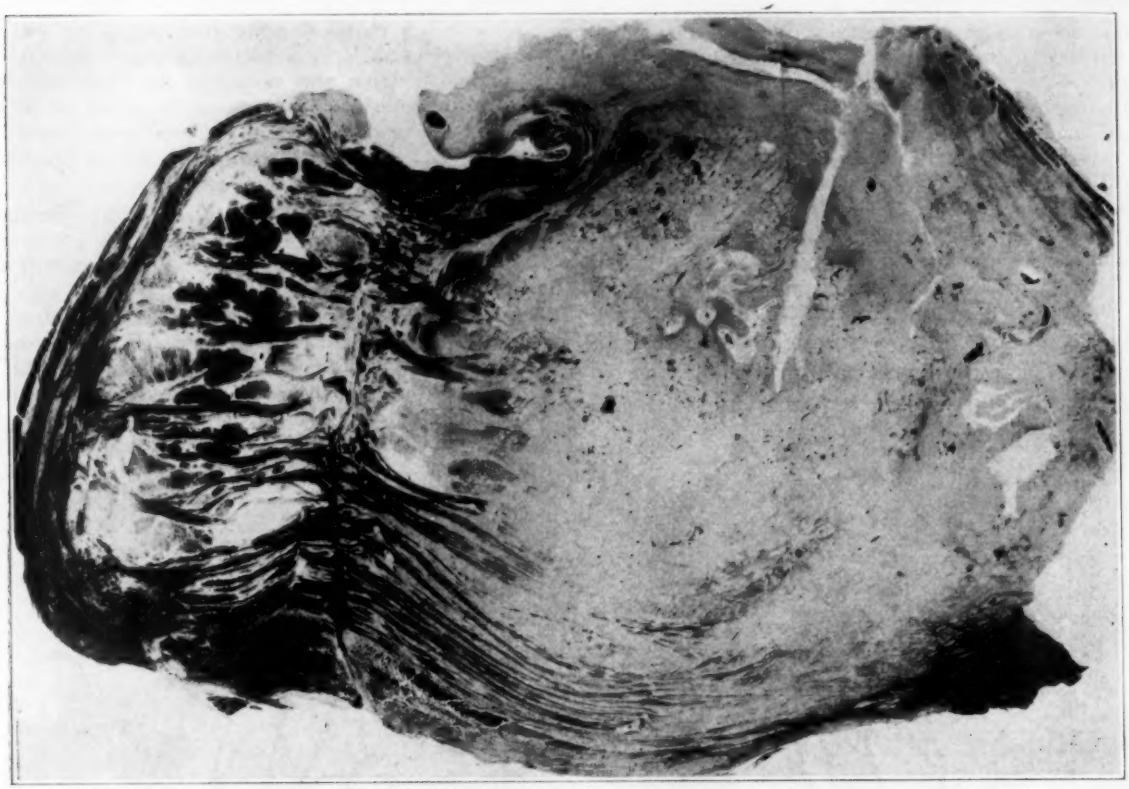

Fig. 5 (case 6).—Glioblastoma multiforme of the brain stem.

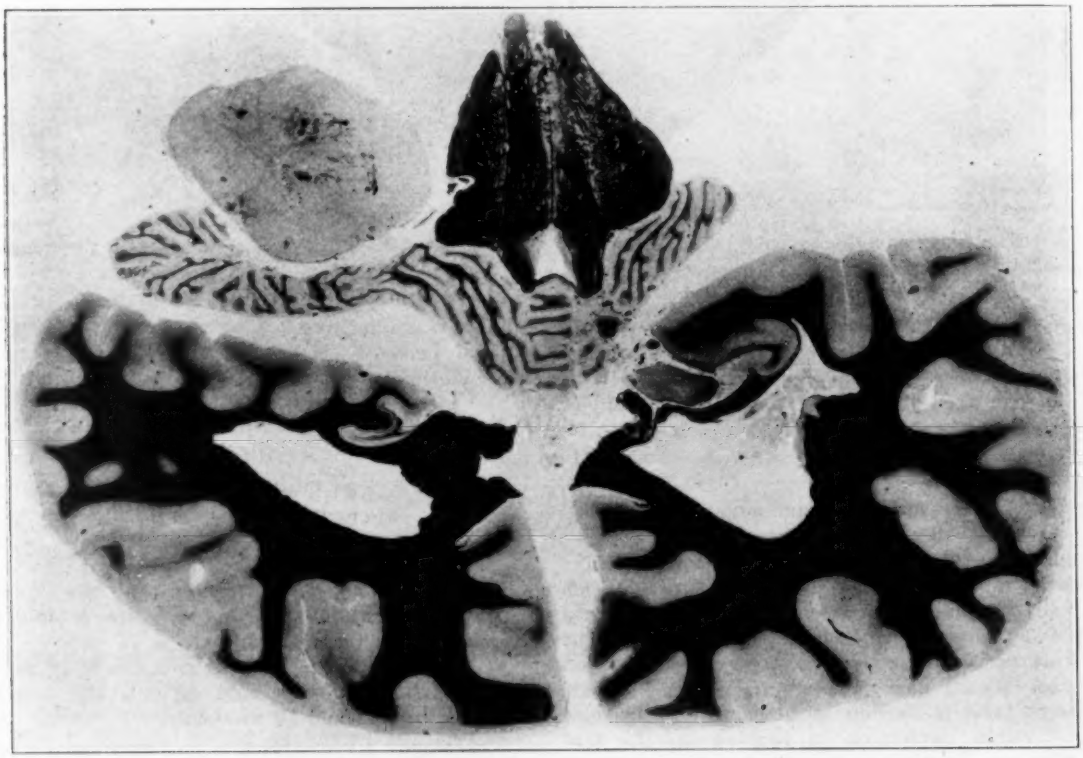

Fig. 6 (case 7).—Meningeal fibroblastoma, compressing the brain stem.

patient became increasingly drowsy, and there developed papilledema, bilateral ophthalmoplegia and clonic movements of the tongue.

Laboratory Data.—Spinal tap showed a clear fluid, a cell count of 30 per cubic millimeter and an initial pressure of 80 mm. of water. The blood chemistry was normal.

Autopsy.—A large tumor was situated on the right side of the pons, destroying the greater part of it (fig. 5). On the right side, the brachium conjunctivum, the posterior longitudinal bundle, the medial and lateral lemnisci and other parts of the mesencephalon were compressed. The aqueduct of Sylvius, although distorted, was not obstructed, and there was no ventricular dilatation. The nerve cells of the nuclei of the various ocular nerves and of the vegetative nervous system showed pathologic changes. The nerve cells of the hypothalamus stained well.

Comment.—The compression of the descending hypothalamic pathways was probably the cause of the lethargy. The increased intracranial tension, as evidenced by the papilledema, did not appear until death, whereas the lethargy was present long before this.

CASE 7.—*Meningeal fibroblastoma of the left cerebellopontile angle with compression of the metencephalon. Nystagmus; somnolence. Increased intracranial pressure.*

S. S., a woman aged 58, gave a history of headaches, gradually increasing visual impairment, personality changes and somnolence, from which she could be aroused.

Neurologic Examination.—Examination disclosed a semistuporous state, from which she could be aroused; pronounced impairment in memory, with limitation of speech and comprehension; spastic quadriplegia, more marked on the right side, with bilateral hyperreflexia and pathologic reflexes; dilated pupils, the right being larger than the left and both responding sluggishly to light; rotary nystagmus, and marked secondary atrophy of the optic nerve.

Laboratory Data.—The blood chemistry was normal. A spinal tap disclosed 5 lymphocytes per cubic millimeter, a total protein content of 35 mg. per hundred cubic centimeters, and an initial pressure of 220 mm. of water.

Autopsy.—There was a large meningeal fibroblastoma in the left cerebellar hemisphere (fig. 6). The entire ventricular system was extensively dilated. The medulla oblongata was notably distorted and compressed (fig. 6). The various nerve cells, including the vegetative nerve cells, showed all types of pathologic change. The nerve cells of the hypothalamic region appeared normal.

CASE 8.—*Metastatic carcinoma to the cerebellar vermis with compression of the metencephalon. Ocular manifestations. Pathologic evidence of increased intracranial pressure.*

F. E., a man aged 59, with carcinoma of the lung, had sudden onset of hyperthermia, headache, dizziness, nausea, vomiting, cerebellar signs and episodes of lethargy, from which he could be aroused.

Neurologic Examination.—Examination revealed papilledema; dilated pupils, which reacted sluggishly to light; lateral deviation of both eyes; cerebellar signs, involving especially the trunk and head; residual paralysis of the left facial nerve of peripheral type; dysphonia and slight dysphagia, and depressed reflexes in the lower extremities, with a positive Babinski sign on the right.

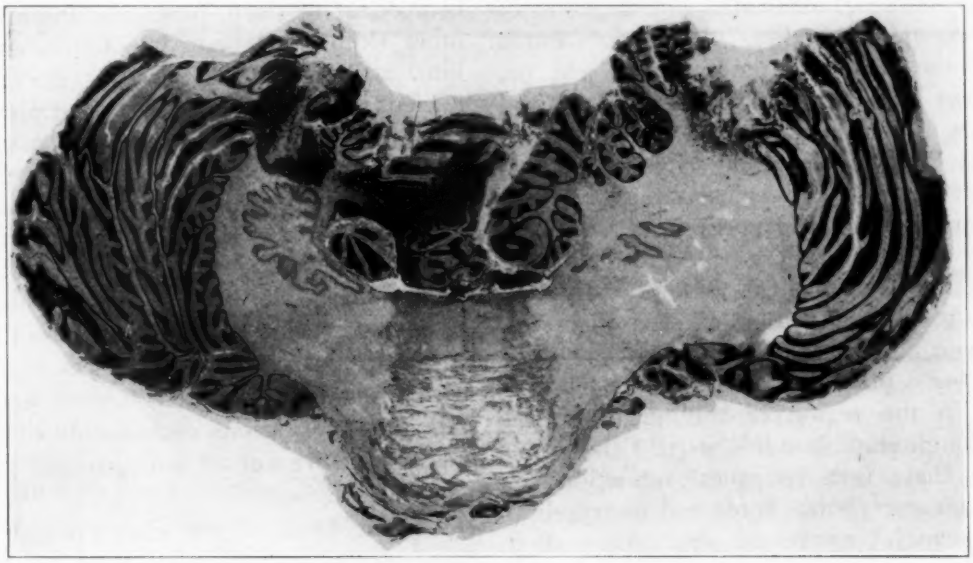

Fig. 7. (case 8).—Metastatic carcinoma to the cerebellar vermis.

Course.—Later, there appeared pronounced rigidity, bilateral forced grasping, episodes of stupor, from which he could still be aroused, and disorientation.

Laboratory Data.—The urea nitrogen of the blood was 17.5 mg. per hundred cubic centimeters. The spinal fluid showed a slight increase in protein and a pressure of 100 mm. of water.

Autopsy.—There was uniform dilatation of the entire ventricular system. Metastatic nodules were present in the vermis cerebelli in the region of the lobulus biventer bilaterally (fig. 7) and in the meninges of the brain stem. The brain stem was compressed. The fourth ventricle was obliterated (fig. 7). Some of the nerve cells of the vagus nerve and those of the vegetative nervous system appeared shadow-like and showed

chromatolysis and slight disintegration. The hypothalamus was normal.

Comment.—The episodes of the lethargy and hyperthermia in this case were undoubtedly caused by the tumor of the posterior fossa obliterating the fourth ventricle and compressing the medulla oblongata.

LESIONS AT MESENCEPHALOMETENCEPHALIC LEVEL

There is some evidence, especially clinical, that somnolence or other disturbances in sleep mechanism may result from lesions at the mesencephalometencephalic level. Righetti [1] (1903), in analyzing 115 cases of gliomas of the posterior fossa with pathologic sleep, found tumors in the region of the medulla oblongata in 28 per cent, tumors of the corpora quadrigemina and epiphysis in 26 per cent and tumors of the cerebellum in 16 per cent. Babonneix and Widiez [2] reported a case of somnolence associated with a glioma of the quadrigeminal bodies. Mikheev [3] found lesions in the region of the thalamus and the periaqueduct gray matter in 5 cases. Mauthner,[4] in 1890, and von Economo,[5] in 1916, induced somnolence by producing experimental lesions in the periventricular gray substance of the third ventricle and neighboring portions of the aqueduct. Marinesco and others [6] concluded that the region around the aqueduct was more directly concerned with the function of sleep than the most anterior portion of the periventricular gray matter. Pötzl [7] placed the center for sleep disturbances in the region of the nuclei of the posterior longitudinal bundles. Rétif [8] stated the belief that there is a reciprocal inhibition between the mesencephalic center and the cerebral cortex. Lucksch [9] expressed the opinion that both the hypothalamus and the neighboring portions of the mesencephalon and thalamus are concerned with sleep but are subject to the control of the cerebral cortex. Hechst [10] stated the belief that the brain stem, the medial part of the posterior third of the thalamus and the contiguous region, comprising the posterior third of the periventricular gray matter and the anterior part of the periaqueductal gray substance, play an equal role in disturbances of sleep.

Many investigators have indicated the relation of lethargy in encephalitis to ophthalmic signs and have attributed the somnolence to involvement of the nuclei of the ocular nerves, which are situated in the mesencephalon and metencephalon. Frank,[11] on the basis of his study on the oculomotor nuclei of mammals, suggested that the pars lateralis of the nucleus subfascicularis belongs to the sleep-regulating center and that in it is localized the most important component of sleep, paresis of the eyelids. Another sleep component, hypotonus, according to him, is localized in the pars dorsalis of the nucleus intraconjunctivalis centralis. Others (von Stockert,[12] Kahn [13]) also asserted that there is a connection between sleep and the ocular mechanisms. Although in all our cases of the mesencephalometencephalic group and in some of the hypothalamic group interference in function of the ocular mechanism was disclosed, the absence of such dysfunction in the other groups and the lack of sleep disturbances in other cases with ocular manifestations would seem to indicate that the various components of the ocular mechanism are not an indispensable part of the sleep mechanism.

On the basis of the experimental and anatomicopathologic observations in some cases, it may be stated that lesions at the junction of the mesencephalon and the diencephalon result in disturbance of the sleep mechanism, especially hypersomnia. It should be remembered that the descending hypothalamic pathways are situated in the mesencephalon and metencephalon. Injury of these structures at this level may result in the same disturbances as injury at their point of origin, that is, in the hypothalamic area.

1. Righetti, R.: Contributo clinico ed anatomopatologica alla studio dei gliomi cerebrali, Riv. di pat. nerv. **8**:24, 1903.

2. Babonneix, L., and Widiez, A.: Gliome des tubercles quadrijuemeaux avec, comme principal symptome, la somnolence, Rev. neurol. **1**:832, 1927.

3. Mikheev, V. E.: On the Anatomical Aspects of the Sleep Problem, J. nevropat. i psikhiat. **24**:75, 1931.

4. Mauthner, L.: Pathologie und Physiologie des Schlafes, Wien. klin. Wchnschr. **3**:445, 1890.

5. von Economo, C.: Ueber den Schlaf, Wien. klin. Wchnschr. (supp.) **38**:1, 1925; Studien über den Schlaf, Wien. med. Wchnschr. **76**:91, 1926; Schlaftheorie, Ergebn. d. Physiol. **28**:312, 1929.

6. Marinesco, G.; Sager, O., and Kreindler, A.: Recherches expérimentales sur le mécanisme du sommeil, Bull. Acad. de méd., Paris **100**:752, 1928.

7. Pötzl, O.: Zur Topographie der Schlafzentren, Monatschr. f. Psychiat. u. Neurol. **64**:1, 1927.

8. Rétif, E.: Le sommeil dissocié: Auto-observation, Rev. neurol. **1**:880, 1927.

9. Lucksch, F.: Ueber das Schlafzentrum, Zentralbl. f. d. ges. Neurol. u. Psychiat. **37**:194, 1924; Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:83, 1924.

10. Hechst, B.: Klinisch-anatomische Beiträge zur zentralen Regulation des Schlaf-Wachseins, Arch. f. Psychiat. **87**:505, 1929.

11. Frank, C.: Intorno alla mia scoperta di due nuclei de mesencefalo dell'uomo ed ulteriori studi sui nuclei oculomotri dei mammiferi, Arch. gen. di neurol., psichiat. e psicoanal. **11**:1, 1940.

12. von Stockert, F. G.: Die Beziehungen der Augenmuskeln zum Schlaf, Med. Klin. **29**:697, 1933.

13. Kahn, W. W.: Sleep and Sleep-Disturbances, J. Michigan M. Soc. **15**:366, 1916.

The two known pathways connecting the hypothalamus and the brain stem are (1) the mamillary peduncle, an afferent pathway of mesencephalic origin, ending chiefly in the lateral mamillary nucleus, and (2) the mamillotegmental tract, an efferent pathway, most likely arising from the dorsal part of the medial mamillary nucleus and terminating in the dorsal tegmental nucleus of the midbrain. An efferent connection demonstrated only physiologically is the vago-supraoptic system.

In our groups, there were 8 cases in which neoplasm occurred at the mesencephalometencephalic level (table). In 4 cases the tumors were situated in the cerebellum and the fourth ventricle; in 3 of these cases the tumor was a hemangioblastoma and in 1 a metastatic carcinoma (cases 1, 2, 3 and 8). In the other 4 cases the tumors were, respectively, spongioblastoma polare of the mesencephalon (case 5), glioblastoma multiforme of the mesencephalon (case 6), medulloblastoma of the metencephalon (case 4) and meningeal fibroblastoma in the cerebellopontile angle (case 7). Compression or invasion of the brain stem was present in all cases. In none was there direct or indirect involvement of the hypothalamus — its nerve cells were normal. Evidence of increased intracranial pressure was present in all cases; in 1 case no clinical evidences but internal hydrocephalus was noted at autopsy. A high incidence of increased intracranial pressure in this group should be expected, as in all cases the neoplasm encroached on the fourth ventricle or the aqueduct of Sylvius. Ocular manifestations, consisting of diplopia, paresis of ocular muscles and nystagmus, were present in all cases; in 2 cases only nystagmus was shown. Endocrine disturbances were absent; 1 patient had loss of libido without any changes in the genitalia. Slight hypothermia was present in 2 cases and hyperthermia in 1 case. Inversion in the sleep mechanism was noted in 1 case. In practically all these cases the descending hypothalamic pathways and the nerve cells of the vegetative system of the brain stem were involved.

Summary of Observations in 8 Cases of Disturbances of Sleep Associated with Mesencephalic and Metencephalic Lesions

	Cases
Hemangioblastoma of cerebellum	3
Metastatic carcinoma to cerebellar vermis	1
Glioblastoma multiforme of mesencephalon	1
Medulloblastoma of metencephalon	1
Meningioma of cerebellopontile angle	1
Spongioblastoma polare of mesencephalon	1
Compression or invasion of brain stem	8
Involvement of hypothalamus	0
Evidences of increased intracranial pressure (in 1, no clinical evidence, but internal hydrocephalus)	8
Ocular manifestations (in 2, only evidence of nystagmus)	8
Endocrine disturbances (in 1, loss of libido without changes in the genitals)	0
Deviation from normal temperature	
Slight hypothermia	2
Hyperthermia	1
Inversion of sleep mechanism	1

SUMMARY AND CONCLUSION

In 8 cases of pathologic sleep there was involvement of the mesencephalon and metencephalon. The hypothalamus was normal in all cases. In all the cases there was implication of the descending hypothalamic pathways and the nerve cells of the vegetative nervous system of the brain stem.

Increased intracranial pressure was present in all cases. The high incidence of increased intracranial pressure in this group should be expected, as in all cases the neoplasm encroached on the fourth ventricle or the aqueduct of Sylvius.

Ocular manifestations, consisting of diplopia, paresis of ocular muscles and nystagmus, were present in all instances; in 2 cases only nystagmus was shown. This phenomenon should be expected because of the location of the nuclei of the oculomotor nerves in this part of the central nervous system. The lack of sleep disturbances in other cases with ocular manifestations would seem to indicate that the various components of the ocular mechanism are not an indispensable part of the sleep mechanism.

Slight hypothermia was present in 2 cases and hyperthermia in 1 case.

From this series of cases, it can be assumed that lesions of the ascending and descending hypothalamic pathways of the mesencephalon (mamillary peduncle and mamillotegmental tract) and some of the vegetative nervous centers in the brain stem result in disturbances of the sleep mechanism.

Montefiore Hospital for Chronic Diseases.

STUDIES IN DISEASES OF MUSCLE

XV. PROGRESSIVE SPINAL MUSCULAR ATROPHY AS A LATE SEQUEL OF ACUTE EPIDEMIC ENCEPHALITIS; REPORT ON TWO CASES

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NEW YORK

Progressive spinal muscular atrophy as a late sequel of acute epidemic encephalitis has been described by several authors, but the possibility of its occurrence is not generally acknowledged. The entity is of interest, not only for a more complete understanding of epidemic encephalitis but for its possible etiologic relationship to certain instances of amyotrophic lateral sclerosis and chronic progressive anterior poliomyelitis. It is for the latter reason that the following 2 cases are reported.

REPORT OF CASES

CASE 1.—*History.*—The patient, a Polish-born salesman, aged 50, was first seen in the New York Hospital on May 14, 1940, complaining of immobility of the face, progressive weakness of the left arm and increasing tremor of both upper extremities. About nine months previously, he first noted tremor, weakness and fatigability of the left upper extremity. At about the same time there developed a severe cramp in the fingers of the left hand, during which the fist was tightly clenched and could not be opened voluntarily. Similar attacks of cramp occurred on two subsequent occasions. About one month after the onset of muscular weakness, the patient's relatives observed that the face lacked its former mobility and expression, that the eyes blinked infrequently and that the mouth hung open. All symptoms progressed steadily, and five months after their onset the patient noted tremor of the right arm and the chin.

The past personal history was significant in that the patient had an acute febrile illness in 1921. For a period of seventeen days he had fever and a sharp, steady pain which radiated from the left shoulder to the hand. During the entire course of the acute illness the patient was unable to sleep, a difficulty which he attributed not to the pain but to loss of ability to fall asleep. He was seen by several neurologists, each of whom diagnosed the condition as acute epidemic encephalitis. After the subsidence of the acute symptoms, the patient had generalized muscular weakness, which gradually improved but which made it necessary for him to be absent from his work for eight months. Thereafter, the patient was entirely free from symptoms until the onset of his present illness, about seventeen years later.

In 1914 he underwent an operation for enucleation of the left eye following injury by a fragment of steel.

From the Departments of Psychiatry and Medicine, Cornell University Medical College and the New York Hospital.

Examination.—The patient was a well developed and obese man. He walked with the left arm extended and held close to the body. The facies was masklike; the eyes blinked infrequently, and the mouth hung open. The voice was of monotonous quality. There were moderate fibrillations and slight atrophy of the tongue. The infraspinatus and deltoid muscles on the left side showed considerable wasting, but the remaining muscles of the left upper extremity, including the small muscles of the hand, were reduced only slightly in volume. All these muscles showed reduction in power that was proportional to the amounts of wasting. There were slight wasting and weakness of the right deltoid muscle. A moderate number of muscular fasciculations were seen over the front of both shoulders and the upper part of the thorax. There was moderate tremor of the fingers of the left hand when the extremity was at rest; when the hand was engaged in purposeful movement, the tremor disappeared. Both upper extremities showed slight rigidity of cogwheel type on passive movement. The tendon reflexes were reduced but equal on the two sides. The remainder of the neurologic examination revealed essentially a normal condition.

Course of Illness from May 14, 1940 to Oct. 18, 1942.—The patient was seen at frequent intervals in the outpatient department. Under a regimen of 0.3 mg. of scopolamine hydrobromide four times daily, there was moderate decrease in muscular tremor and rigidity for about four months, after which time these symptoms increased slowly but steadily. Each time the medication was discontinued or the dosage decreased, the symptoms increased. Progression in muscular disability was steady during the entire period of observation. In January 1941, weakness of the right hand was noted; in March 1941, the patient was barely able to lift the left arm from the side of the body, and in December of the same year, the right shoulder was affected to the extent that the hand could be lifted only as high as the shoulder when the elbow was extended. At about the same time, he began to complain of frequent cramps in the calves and feet at night. Occasionally a "cramp" in the tongue interfered with talking. In February 1942, all the muscles of the shoulder girdle showed considerable wasting, and for the first time definite wasting of the forearms and hands was noted. Fasciculations were absent. The right upper extremity showed definite rigidity of cogwheel type on passive movement, but the left upper extremity, which now hung limp against the side of the body, no longer showed increased resistance to passive stretch. In May 1942, the patient began to complain of edema of the left hand in the evenings. This was relieved to a moderate degree when the hand and forearm were supported by a sling above the level of the waist. In May 1942, Dr. J. Casals,

of the Rockefeller Institute for Medical Research, tested a sample of the patient's blood for complement-fixing antibodies against antigens of eastern and western equine encephalomyelitis, St. Louis encephalitis and lymphocytic choriomeningitis. The reactions to all tests were negative. In September 1942, the patient began to have considerable dyspnea and orthopnea and found it necessary to use two pillows at night. On Oct. 18, 1942, he was admitted to the New York Hospital for further investigation.

Second Examination.—The following neurologic signs were present: masklike immobility of the facies; coarse

Fig. 1. (case 1).—*A*, drooping jaw, partial protrusion of tongue and immobile facies characteristic of paralysis agitans. *B*, wasting of muscles of the shoulders and upper portion of the arms.

tremor of the jaw; moderate atrophy, fibrillary twitchings and coarse tremor of the tongue; difficulty in phonation; monotonous speech; considerable wasting of the muscles of the shoulder girdle and of both upper arms, which was more advanced on the left side; moderate atrophy of the muscles of the forearms and hands; fasciculations of the muscles of both shoulders and upper extremities; gross spasms of the muscles of both calves, and fasciculations of the muscles of both thighs. The patient was practically unable to make any voluntary movement with the left upper extremity and could raise the right arm only as high as the level of the shoulder. Resistance to passive stretch was diminished in both upper extremities. Muscular power was slightly reduced in the lower extremities, where resistance to passive stretch was slightly increased. The tendon reflexes in the upper extremities were absent except for the biceps reflex, which could barely be elicited. The deep reflexes in the lower extremities were exaggerated, but ankle clonus was absent and the plantar response was of flexor type bilaterally. The superficial abdominal and cremasteric reflexes were active and equal on the two sides. There were no sensory defects.

In addition, the blood pressure was elevated; the systolic pressure was 154 and the diastolic 112 mm. of mercury. The heart was moderately enlarged, but there were no murmurs.

Examination of the blood showed 5,300,000 red cells per cubic millimeter, 18.9 Gm. of hemoglobin per hundred cubic centimeters and 10,800 white cells per cubic millimeter, with a normal differential count. The Kline reaction of the blood was negative. The concentrations of calcium, phosphorus, potassium, sodium and uric acid in the serum were 10.1, 3.8, 16, 335 and 3.2 mg. per hundred cubic centimeters, respectively. The phosphatase activity of the blood was 2.8 Bodansky units.

The spinal fluid was under normal pressure and contained no cells. The concentrations of sugar, chlorides and protein in the spinal fluid were 61, 580 and 30 mg. per hundred cubic centimeters, respectively. The Wassermann reaction was negative, and the colloidal gold curve was normal.

Two dextrose tolerance tests gave essentially normal results except that the level of the blood sugar determined three and a half hours after ingestion of the dextrose was low (45 and 55 mg. per hundred cubic centimeters). The circulation time of the blood was nineteen seconds. Venous pressure in the right arm was 9 cm. of water. The basal metabolic rate was +14 per cent.

Roentgenograms of the skull and of bones of the extremities revealed no pathologic changes. Fluoroscopic examination of the thorax showed that the diaphragm was high on both sides, extending to the level of the third anterior intercostal space on the right side and to the fourth intercostal space on the left side. No movement of the diaphragm was seen on repeated respiration.

About one week after his admission the muscular cramps gradually disappeared. The patient was discharged from the hospital on Nov. 2, 1942.

Subsequent Course.—During the next seven months the patient was seen on several occasions, when steady progression in muscular wasting was noted. In February 1943, he again began to complain of cramps in the calves, and the right hand was found to be much weaker. In May of the same year, the patient had increasing difficulty in respiration. In June, weakness of all four extremities was increased; muscular cramps, which occurred nightly, were severe, and speech was indistinct. The following month the patient died of paralysis of the respiratory muscles.

CASE 2.—The patient, a male bank clerk, aged 34, was first seen in the New York Hospital on Sept. 19,

1943, with the complaint of weakness and wasting of the arms and legs.

In 1924 he had a severe febrile illness, which was diagnosed as acute epidemic encephalitis. After a period of two weeks, during which he was delirious, the illness gradually subsided, and the patient appeared to have recovered completely. He had good health until nine years later, when he began to complain of increasing weakness of the right arm, which was followed in a few months by similar disability in the left arm. At about the same time he noted frequent "twitchings" in the muscles about the shoulders and observed gradual diminution in volume of the upper portion of the arms. The weakness and wasting progressed slowly but steadily and extended to all the muscles of the upper extremities. Eight years after the onset of muscular weakness in the arms, the patient began to fall often, owing to sudden "buckling up" of the knees. A few months later, increasing difficulty in walking, in climbing stairs and in getting up from a sitting position was noted. Fasciculations, similar to those in the upper extremities, were seen in the thighs.

The past personal and family histories were noncontributory.

Examination.—The patient swayed from side to side while walking; the trunk slumped forward, and the arms hung limply at the sides of the body. He was unable to sit up from a lying-down position without using his arms as supports. The pupils, the extraocular movements and the fundi were normal. There was no facial weakness. The tongue was without atrophy or adventitious movements. The muscles of the neck were of good power. Both scapulas showed definite winging. There was advanced wasting of all the muscles of the upper extremities, with diminution in power which was proportional to the wasting. The hands were of main en griffe type. The biceps and triceps reflexes could not be elicited. No adventitious movements were seen in the muscles of the upper extremities. The superficial abdominal reflexes were absent. There were moderate wasting and weakness of the muscles of the thighs, but the muscles of the calves and feet were of normal volume and power. Occasional fasciculations were seen in the thighs, but all muscles below the knees were without adventitious movements. The patellar and achilles reflexes were sluggish but equal on the two sides. There was no ankle clonus. The plantar reflex was of flexor type bilaterally. There was no increase in resistance to passive stretch in any of the extremities. Sensibility for pain, light touch, temperature, vibration and position was normal. There were no signs suggestive of paralysis agitans.

COMMENT

Both patients had a severe attack of acute epidemic encephalitis, from which they appeared to recover completely. One of them had severe pain in an upper extremity, but neither showed evidence of involvement of motor nerves during the acute illness. Several years after the attack of acute encephalitis, both patients presented muscular fasciculations and progressive wasting, which began in the muscles about the shoulders but later affected other groups. One patient had paralysis agitans, which had its onset at about the same time as the muscular atrophy.

One patient is still alive, ten years after onset of muscular symptoms; in the other signs of bulbar involvement developed, and he died four years after muscular wasting first was noted.

Muscular paralysis is not unusual during the acute stage of epidemic encephalitis. However, progressive muscular wasting of the types commonly seen with progressive anterior poliomyelitis and amyotrophic lateral sclerosis is relatively rare.

Progressive spinal muscular atrophy has been observed to occur in the following three circumstances: (1) during a chronic phase of epidemic encephalitis; (2) shortly after the initial acute attack of epidemic encephalitis has subsided, and (3) after a long interval, of several months or years, following apparent complete recovery from the acute infection.

Froment and Gennevois [1] reported a case of unilateral muscular atrophy of Aran-Duchenne type in a woman who had had an attack of "grip" six months before the onset of muscular symptoms. In the case of Gutmann and Kudelski [2] there developed muscular wasting resembling dystrophy of fascioscapulohumeral type one and a half months after a severe attack of epidemic encephalitis, which was associated with an intense "crawling" sensation in the cervical and scapular areas. Froment [3] reported the case of a woman aged 24 who had encephalitis, with continuous low grade fever for several months, during which period there were progressive muscular wasting, exaggerated reflexes, fasciculations and myoclonus. Bulbar signs developed, and the patient died within three years from onset of the illness. The anatomic lesions were characteristic of amyotrophic lateral sclerosis. Sicard and Paraf [4] stated that they had seen 6 cases of muscular atrophy with fasciculations associated with chronic epidemic encephalitis; however, in all instances the wasting was localized to a few muscular groups and improved steadily. The authors expressed the opinion that in epidemic encephalitis the process can extend to the spinal cord, spinal roots and

1. Froment, J., and Gennevois, E.: Atrophie musculaire progressive myélopathique et encéphalomyélite myoclonique, Rev. neurol. **28**:726, 1921.

2. Gutmann, R. A., and Kudelski: Encéphalite léthargique datant de cinq ans avec séquelles myopathiques à type Landouzy-Dejerine, Bull. et mém. Soc. méd. d. hôp. de Paris **45**:24, 1921.

3. Froment, J.: Sclérose latérale amyotrophique et encéphalite épidémique, Rev. neurol. **32**:842, 1925.

4. Sicard, J. A., and Paraf, J.: Encéphalites amyotrophiques, de type radiculaire ou péripherique, Bull. et mém. Soc. méd. d. hôp. de Paris **44**:1289, 1920.

peripheral nerves. Netter [5] postulated that the virus of epidemic encephalitis can affect various parts of the central and peripheral nervous system. The patient of Guillain and Alajouanine [6] had muscular atrophy of the upper extremities, exaggerated tendon reflexes, bulbar signs and many features of paralysis agitans. Three years before the onset of muscular symptoms the patient had had a severe attack of encephalitis, with insomnia for two months and severe pains in the upper portion of the arms and the scapular areas. Euzière, Pagès and Janbon [7] reported a case of progressive muscular atrophy of six years' duration, which had its onset immediately after an acute attack of epidemic encephalitis. The authors designated the condition as "chronic epidemic encephalitis in a form of anterior poliomyelitis." Carr [8] observed a man aged 29 who had encephalitis with diplopia, followed by somnolence, intermittent diplopia and soreness of the muscles for three years. Examination seven years after the acute infection showed wasting and fasciculations of the muscles of the shoulder girdle. Wimmer [9] reported 5 cases of amyotrophic lateral sclerosis subsequent to chronic epidemic encephalitis. In 2 of these cases muscular wasting followed almost immediately the initial stage of the infection. In two later reports, Wimmer [10] gave a summary of 20 cases of spinal muscular atrophy in patients with a previous history of encephalitis. In 2 of these cases the muscular wasting was most pronounced in the proximal groups. Of the entire series of 20 patients, 4 had paralysis agitans. Jancsó,[11] Nyssen and van Bogaert [12] and Ornsteen [13] reported instances of amyotrophic lateral sclerosis following epidemic encephalitis. The patient of Illing [14] noted muscular stiffness and drooling of saliva four years after an attack of acute encephalitis. Seven years after the acute infection there were stiffness of various muscle groups and wasting of the hands. The condition progressed steadily, and three years later the hands were of the main en griffe type. The muscles of the shoulder and pelvic girdle were without wasting. The author expressed the opinion that this was an instance of epidemic encephalitis with subsequent paralysis agitans and extension of the process to the spinal cord. Yealland's [15] patient had slowly progressive weakness of ten years' duration and tremor of Parkinson's type for four years. There was no history of an acute infection. The patient of Lhermitte, Thibault and Ajuriaguerra [16] gave a history of paralysis agitans immediately following a typical attack of acute encephalitis. Seven years later amyotrophic lateral sclerosis developed. The course was progressive until his death, thirteen years after the acute attack of encephalitis. Although the clinical picture resembled that of typical amyotrophic lateral sclerosis, as described by Charcot, there were notable histologic differences. The degenerative changes in the spinal cord were not as uniform in their intensity as are found in typical cases. The tracts of Flechsig and Gower were more affected than were the crossed pyramidal tracts, and the posterior tracts were intact. The cells of the anterior horns were reduced in number and size. Decourt, Mathieu and Meyer [17] and Khait [18] reported on patients

5. Netter, in discussion on Sicard and Paraf.[4]

6. Guillain, G., and Alajouanine, T.: Sclérose latérale amyotrophique avec contracture intense du type extrapyramidal (hypertonic plastique et exagération des réflexes de posture): Discussion de son étiologie encéphalitique, Rev. neurol. **33**:337, 1926.

7. Euzière, J.; Pagès, P., and Janbon, M.: Poliomyélite antérieure chronique consécutive à une névraxite épidemique, Bull. Soc. sc. méd. biol. Montpellier **7**:85, 1926; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **44**:80, 1926.

8. Carr, A. D.: An Encephalitic Residual Simulating Progressive Muscular Atrophy of Shoulder Girdle Type, Arch. Neurol. & Psychiat. **16**:344 (Sept.) 1926.

9. Wimmer: Amyotrophies de type sclérose latérale amyotrophique dans l'encéphalite épidémique chronique, Rev. neurol. **32**:841, 1925.

10. Wimmer, A., and Neel, A. V.: Les amyotrophies systématisées dans l'encéphalite épidémique chronique, Acta psychiat. et neurol. **3**:319, 1928. Wimmer, A.: Les amyotrophies systématisées dans l'encéphalite épidémique chronique, Acta med. Scandinav., 1928, supp. 26, p. 392.

11. Jancsó, S.: Ueber ein nach Encephalitis epidemica beobachtetes, der amyotrophischen Lateralsklerose ähnliches Krankheitsbild, Klin. Wchnschr. **7**:2442, 1928.

12. Nyssen, and van Bogaert, L.: Forme médullaire de l'encéphalite épidémique chronique, J. d. neurol. et psychiat. **28**:114, 1928.

13. Ornsteen, A. M.: The Syndrome of Amyotrophic Lateral Sclerosis in Epidemic Encephalitis, J. Nerv. & Ment. Dis. **82**:369, 1930.

14. Illing, E.: Uebergreifen der Encephalitis lethargica auf das Rückenmark, Monatschr. f. Psychiat. u. Neurol. **82**:177, 1932.

15. Yealland, L. R.: Progressive Muscular Atrophy Associated with Paralysis Agitans, Proc. Roy. Soc. Med. **31**:211, 1938.

16. Lhermitte, L.; Thibault, and Ajuriaguerra: Syndrome de sclérose latérale amyotrophique d'origine encéphalitique, Rev. neurol. **45**:372, 1938.

17. Decourt, J.; Mathieu, P., and Meyer, L.: Syndrome de sclérose latérale amyotrophique consécutif à une encéphalite léthargique; signes extrapyramidaux associés, Rev. neurol. (pt. 2) **41**:596, 1934.

18. Khait, M. B.: Syndrome of Amyotrophic Lateral Sclerosis Developing After Epidemic Encephalitis, Sovet. psikhonevrol. (nos. 4-5) **15**:85, 1939; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **97**:400, 1940.

with amyotrophic lateral sclerosis following epidemic encephalitis. Both patients showed evidence of involvement of the extrapyramidal system.

More recently, Wechsler, Sapirstein and Stein [19] reported 2 cases of amyotrophic lateral sclerosis immediately following acute infection of the nervous system.

Numerous authors, including Matzdorff [20] and Poussepp and Rives,[21] have expressed the opinion that in some cases of amyotrophic lateral sclerosis there is evidence that the process is of infectious origin. While there appears to be little doubt that the spinal cord can be involved early in an attack of epidemic encephalitis (Kraus,[22] Calhoun,[23] Grinker,[24] Mingazzini,[25] Gross,[26] Stern [27] and Cruchet and Verger [28]), evidence for the occurrence of amyotrophic lateral sclerosis as a sequela several years after the acute infection is less convincing. However, the cases which are reviewed in this report and the data in my first case indicate the strong probability of such an occurrence. It appears that involvement of various parts of the nervous system in acute epidemic encephalitis may not be as unusual as is commonly assumed. As a matter of fact, in their studies on "spring-summer encephalitis" in Russia, Robinzon and Sergeeva [29] regularly found diffuse involvement of the entire nervous system, especially of the anterior horn cells of the upper spinal segments. Whether this early involvement of the anterior horn cells and other structures of the spinal cord during the acute infection is related to subsequent degenerative changes of amyotrophic lateral sclerosis or chronic anterior poliomyelitis can only be speculated on at present.

19. Wechsler, I. S.; Sapirstein, M. R., and Stein, A.: Primary and Symptomatic Amyotrophic Lateral Sclerosis: A Clinical Study of Eighty-One Cases, Am. J. M. Sc. **208**:70, 1944.

20. Matzdorff, P.: Zur Pathogenese der amyotrophischen Lateralsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:703, 1925.

21. Poussepp and Rives: Contribution à la pathologie et á la pathogénie de la sclérose latérale amyotrophique, Rev. neurol. **32**:834, 1925.

22. Kraus, W. M.: An Unusual Case of Epidemic Encephalomyelitis, J. Nerv. & Ment. Dis. **52**:142, 1920.

23. Calhoun, H. A.: Histopathology of the Brain and Spinal Cord in a Case Presenting a Postinfluenzal Lethargic Encephalitis Syndrome, Arch. Neurol. & Psychiat. **3**:1 (Jan.) 1920.

24. Grinker, J.: Report of an Unusual Case of Lethargic Encephalitis, J. Nerv. & Ment. Dis. **52**:323, 1920.

25. Mingazzini, G.: Klinischer und anatomisch-pathologischer Beitrag zum Studium der Encephalitis epidemica (lethargica), Ztschr. f. d. ges. Neurol. u. Psychiat. **63**:199, 1921.

26. Gross, W.: Ueber Encephalitis epidemica, Ztschr. f. d. ges. Neurol. u. Psychiat. **63**: 299, 1921.

27. Stern, F.: Encephalitis Epidemica, Fortschr. d. Neurol., Psychiat. **1**:205, 1929; cited by Illing.[14]

28. Cruchet, R., and Verger, H.: Les formes basses de l'encéphalomyélite épidémique, myélites, radiculites, polynévrites, Presse méd. **34**:737, 1926.

29. Robinzon, I. A., and Sergeeva, J. I.: Pathologo-Anatomical Changes in the Nervous System Associated with Spring-Summer (Forest) Encephalitis, Arch. biol. nauck **56**:71, 1939; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **97**:9, 1940.

SUMMARY

Two cases of progressive muscular atrophy with onset several years after an attack of acute epidemic encephalitis are reported. In 1 instance the clinical picture was that of chronic anterior poliomyelitis; in the other the changes were those of amyotrophic lateral sclerosis and paralysis agitans.

525 East Sixty-Eighth Street (21).

News and Comment

SECOND SOUTH AMERICAN CONGRESS ON NEUROSURGERY

The second South American Congress on Neurosurgery will be held in Santiago, Chile, in April 1947.

The following subjects have been assigned to the various neurosurgical groups in Argentina, Brazil, Chile, Peru and Uruguay:

1. Hydrocephalus: (*a*) Classification, Peru; (*b*) Pathology, Argentina; (*c*) Clinical aspects, Brazil; (*d*) Treatment, Argentina.

2. Histology of Brain Tumors in Relation to Clinical Symptoms: (*a*) Pathology and clinical course, Argentina; (*b*) Pathology and surgical treatment, Argentina; (*c*) Pathology and radiotherapy, Uruguay.

3. Brain Abscess: (*a*) Pathology, Uruguay; (*b*) Clinical aspects of cerebral abscess, Brazil; (*c*) Clinical aspects of cerebellar abscess, Argentina; (*d*) Treatment, Chile.

The program will also provide time for open discussions, practical demonstrations and moving picture projections.

Inquiries may be directed to: Dr. Alfonso Asenjo, Director, Central Institute of Neurosurgery, Santiago, Chile.

REFRESHER COURSE IN PSYCHIATRY AND NEUROLOGY, NEW YORK UNIVERSITY COLLEGE OF MEDICINE

Beginning Sept. 17, 1946, an eight weeks' full time refresher course in psychiatry and neurology will be given for physicians at the New York University College of Medicine, Psychiatric Pavilion, Bellevue Hospital, New York. Instruction will be given by the staffs of the psychiatric and neurologic departments of the medical college, with the assistance of staff members from other divisions of the medical school. The subjects covered will include clinical psychiatry, clinical neurology, functional and organic psychoses, psychoneuroses, psychopathology, therapy, psychosomatic problems, neuroanatomy, neurophysiology, neuropathology, roentgenologic diagnosis, electroencephalography and other related subjects.

Registration is open to graduates of approved grade A medical schools who have completed an approved internship in medicine. Preference will be given to applicants who have had previous approved psychiatric training and to those who are preparing for examination by the American Board of Psychiatry and Neurology.

Early application on an approved form for registration is recommended because of the limited enrolment which can be accommodated. The tuition fee is $250.

Additional information may be obtained from Dr. S. Bernard Wortis, professor of psychiatry, New York University College of Medicine, 477 First Avenue, New York City 16.

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

A new publication, the *Quarterly Review of Psychiatry and Neurology,* under the editorship of Dr. Winfred Overholser, professor of psychiatry, George Washington University School of Medicine, and superintendent of St. Elizabeths Hospital, is being launched by the Washington Institute of Medicine. Like the quarterly reviews in other fields of medicine published by the Washington Institute, this publication will consist of abstracts of articles of psychiatric and neurologic interest from journals from all parts of the world. The annual subscription is $9.

OFFICIAL METHOD OF RECORDING PSYCHIATRIC DIAGNOSES AND REVISED NOMENCLATURE ADOPTED BY UNITED STATES ARMY

The Army has adopted for its official use a new method of recording a psychiatric diagnosis and a revised nomenclature, as set forth in War Department Technical Medical Bulletin, No. 203, dated Oct. 19, 1945. This was adopted after an extensive study during 1944 and 1945, during which time suggestions were obtained from a large number of leading civilian and military psychiatrists.

This Bulletin will prove valuable as a means of standardizing terminology in hospital, clinic and private practice. In many ways it resembles the "Standard Nomenclature of Disease" but, in addition, presents criteria of diagnosis in psychiatric conditions. It may be obtained from the Superintendent of Documents, Washington, D. C.

PROJECT IN INTERNAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE

Cornell University Medical College annonuces a project in internal medicine at the New York Hospital, designed to deal clinically and experimentally with psychosomatic patients. There are three main objectives: (1) to develop a practical method of dealing with ambulatory clinic patients who suffer from symptoms related to their emotional states and life situations, (2) to engage in experimental study of the mechanisms involved in illness of this nature and (3) to train especially able young physicians in experimental methods and a critical psychosomatic approach to the care of the sick. Approximately half of the time will be spent in the diagnosis and management of patients and half of the time in research dealing mainly with mechanisms underlying symptoms.

The project will be directed by Dr. Harold G. Wolff with the assistance of an internist, Dr. Stewart Wolf; a psychiatrist, Dr. Herbert S. Ripley Jr., and six fellows. Fellows will be appointed for a period of one year, with the expectation of serving for two years or more. Their salary for the first year will be $2,500. Candidates for fellowships should have at least two years' training in internal medicine and have given evidence of a psychiatric orientation. They need not have had experience in research but must have a serious interest in investigation, energy and curiosity.

Prospective candidates should arrange for a personal interview through Dr. David P. Barr, professor of medicine, the New York Hospital, 525 East 68th Street, New York.

Obituaries

PETER BASSOE, M.D.

1874-1945

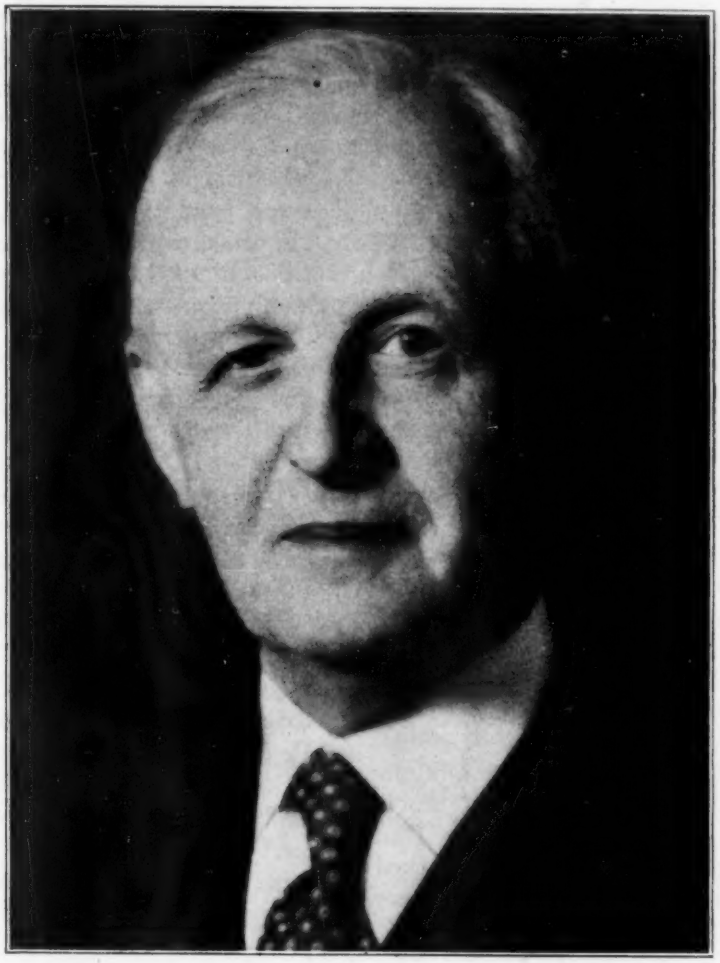
Peter Bassoe was born May 18, 1874, at Drammen, Norway, the son and grandson of Lutheran ministers. His father was beloved by his congregation but was impractical and improvident; his mother was rather dogmatic and apt to make a scene when opposed; these facts are of importance in evaluating his subsequent career. After completing the Cathederal School in Oslo, he came to America, at the age of 19 years. He had a relative in Chicago; but when he arrived here, in the midst of a depression, in 1893, he found this relative out of work and more in need of assistance than himself. So he moved on to the home of his father's cousin, the Rev Dr. Laur. Larsen, president of Luther College, Decorah, Iowa. There he began teaching country school, boarding around in the manner of those times. The following year he entered the old College of Physicians and Surgeons in Chicago, assisting in chemistry and working at any odd jobs he could find to pay for his schooling. When he graduated, in 1897, he took the competitive examination for interns at the Cook County Hospital and made first place. The following year found him assistant physician in the state hospital at Mount Pleasant, Iowa, and two years later he went to the state hospital in Worcester, Mass., where he worked with Adolf Meyer. In 1901 he made a trip to Europe. After a brief stay in Heidelberg and Montpellier, he moved on to Prague, where he fell seriously ill with nephritis. He returned to Chicago in 1902 and occupied a position as pathologist at the Presbyterian Hospital, with which institution he was to remain associated until his death. In 1906 he again went to Europe, this time to Berlin, Paris and London, where he visited the neurologic clinics. On returning to this country, in 1907, he became attending neurologist to Cook County Hospital and assistant to Dr. Hugh T. Patrick. He was also placed on the staff of the Presbyterian Hospital, as assistant attending neurologist, and on the faculty of Rush Medical College, as assistant professor of nervous diseases. Thus, he was definitely launched on his career; his formal student days were over but he never ceased to study; his thirst for knowledge ended only with his last breath. The struggle to obtain an education was hard, and he could expect only moral support from Dr. Larsen, who had a large family to support on a meager salary. He was wont to relate interesting experiences with free lunch counters during this period.

In 1907, also, he married Miriam Gardner, who had just graduated from Rush Medical College. I doubt that she could have been more useful to society as a practitioner of medicine than as Mrs. Bassoe. At least her husband had no qualms of conscience at ruining a good physician. He remarked often on his good fortune in finding the perfect helpmeet, one, moreover, so gracious, equable and amiable as to make his home a haven of rest and recuperation from the worries and strains of his professional life. He was grateful for his contrast with his home life during his boyhood, as, indeed, he was grateful for all the blessings which came his way. As his family grew in numbers, he moved to Evanston, where his friends knew him in the big, rambling house on Michigan Avenue, which always seemed to be the perfect setting for him. His main relaxation was caring for its grounds and garden. He had little interest in the fine arts, and it was difficult to get him out for anything except a medical meeting or a serious lecture on some instructive subject. He also did not care much for games, although some one taught him to pitch horseshoes, and many a pleasant game we had until his weakened heart made even this mild exertion inadvisable.

As is too often the case with suburbanites, he had not much time for local civic affairs, leaving such matters to his wife, who was for many years a member of the school board; the town was too far from the office and hospitals where his practice was carried on. The long journey to and from his work left him little time, and this he spent in writing and in reading and abstracting the current literature of neurology and psychiatry. In 1910 he became associated with Dr. Patrick in editing the "Year Book of Neurology," and in 1918 he took over the sole editorship, which he held until an illness in 1933 caused him to relinquish it. In this role he initiated the policy of writing pithy prefaces to

Read at a meeting of the Illinois Psychiatric Society, Chicago, Dec. 6, 1945.

the yearly summaries, a practice which his successor, Dr. Hans Reese, has continued and amplified. In this work he was greatly aided by his wife and, later, by his daughters, who still remember their pride as they became old enough, one by one, to help their father in this way. It was in this occupation that his thorough knowledge of neurology was built up and maintained. He was constantly alert to all the latest developments in his field; an example of it was his prompt recognition of epidemic encephalitis in 1918.



PETER BASSOE, M.D.
1874-1945

Dr. Bassoe had an erudite mind. He was a pioneer in neuropathology in the Middle West, and most of his writings are of a clinicopathologic nature, for which his experience as pathologist so well fitted him. He took little part in the development of histopathology except as collaborator with others, notably Hassin and Grinker, being handicapped by the demands of a busy practice and by working in an institution in which the neurologist was a mere adjunct to the medical clinic. It is true that there was a neuropathologic laboratory, but its equipment was antediluvian, and it was dominated by a physician who seemed interested mainly in conducting a graveyard for brains. By the time Dr. Bassoe came to the leadership of the laboratory and clinic he was already ill and advanced in years.

His medical writings include over 100 titles, the first one published in 1898, while an intern in the Cook County Hospital. Probably the most important of them are his careful studies of caisson disease and of the triad of acromegaly, gigantism and dwarfism.

In his last years he became interested in medical history and wrote useful accounts of the development of neurology and psychiatry in Chicago and the Middle West. He had also become much interested in Mexico; he spent several vacations there and learned Spanish, and this led him to an interesting study of the early care of psychiatric patients in Spain.

He was very sociable and loved to go to medical meetings, where his quizzical smile and

quaint drawl, which he never quite lost, were familiar. He was no puritan and took a drink with the boys, but never more than he could hold, and, when the stories began to descend below the belt line, he would quietly transfer himself to a company which still retained its dignity. Tolerance and moderation were his marked characteristics. His early experiences at home gave him a distaste for public controversy. He was a courageous man and staunchly supported his ideals, but rarely did he make an open frontal attack. His quiet scorn was sometimes effective, but his favorite method was simply to start something better. An example of this approach is the founding of the Central Neuropsychiatric Association.

In 1911 he was elected to the American Neurological Association, where he had a chance to see how that organization was dominated by the Atlantic seaboard. The meetings were always held along the Atlantic coast, causing much inconvenience and expense to neurologists west of the Alleghanies. This situation had often been discussed, but it remained for Bassoe to do something about it. In St. Louis, in 1922, he gathered a group of neuropsychiatrists and proposed the organization of a Central Neuropsychiatric Association, which should hold its meetings in rotation in various cities, thus making it possible for the membership to become better acquainted with the various clinics, and so serve as a stimulus to the local group. He was elected first president of the organization, which claims the allegiance of an increasingly friendly and enthusiastic membership, of which he was one of the most faithful.

He was aware of the unsatisfactory conditions in the state hospitals for the insane in Illinois but did not tilt at windmills, like that Don Quixote of psychiatry, Clevenger. He worked quietly and persistently, nevertheless, to improve conditions, being a member of Governor Horner's committee which drew the plans for the establishment of the Illinois Neuropsychiatric Institute. After the affiliation of the Presbyterian Hospital with the University of Illinois, he promptly transferred his outpatient department to the Institute and faithfully attended its staff conferences.

Dr. Bassoe was primarily a physician—painstaking, solicitous and tireless in the care of his patients. He examined them carefully and had an amazingly accurate memory for the details of their illnesses. None needed to tell him that the physician must treat the patient as well as the illness; he knew this by instinct.

His professional activity centered around the Presbyterian Hospital and the Central Free Dispensary, but he was, at one time or another, on the staff of numerous hospitals in Chicago and its vicinity, including the Rogers Memorial Sanitarium at Oconomowoc, Wis., of which he was a trustee. During World War I he was a contract surgeon and later was consulting neuropsychiatrist of the United States Public Health Service, from 1918 to 1922.

He was a modest man; yet many honors came to him. In 1904 he was president of the Chicago Scandinavian-American Medical Association; in 1908, president of the Chicago Pathological Society; in 1911, president of the Chicago Neurological Society; in 1922, president of the Central Neuropsychiatric Association and Chairman of the Section on Nervous and Mental Diseases of the American Medical Association; in 1927, president of the American Neurological Association; in 1930, president of the Association for the Study of Internal Secretions, and in 1936, president of the Institute of Medicine of Chicago. He was an honorary member of the Neurological Society of Norway and of the Swedish Medical Association.

Peter Bassoe died of coronary thrombosis on Nov. 5, 1945. He was universally beloved. His friendly presence and sober counsel will be sorely missed by all who knew him. He was the sort of able and honorable immigrant, hundreds of whom came to this country in search of better opportunities than they could find in their homelands and remained to strengthen and enrich it. Would that we had more of them!

PERCIVAL BAILEY, M.D.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

NEUROSECRETION: VI. A COMPARISON BETWEEN THE INTERCEREBRALIS-CARDIACUM-ALLATUM SYSTEM OF THE INSECTS AND THE HYPOTHALAMO-HYPOPHYSEAL SYSTEM OF THE VERTEBRATES. B. SCHARRER and E. SCHARRER, Biol. Bull. **87**:242, 1944.

The hypothalamohypophysial system in vertebrates is in many respects similar to the pars intercerebralis–corpus cardiacum–corpus allatum system in insects. In vertebrates, the hypothalamic nuclei innervating the pars nervosa of the pituitary gland contain secreting nerve cells. In insects, the pars intercerebralis of the protocerebrum contains neurosecretory cells. On the basis of these morphologic relationships, the hypothalamic nuclei and the pars nervosa of the hypophysis appear as one, closely interconnected system. Likewise, the pars intercerebralis and the corpus cardiacum of insects may be viewed as one neuroendocrine complex rather than as two separate sources of hormones.

COBB, Boston.

THE ARCHITECTURE OF THE CEREBRAL CAPILLARY BED IN LUNGFISHES. E. HORNE CRAIGIE, J. Comp. Neurol. **79**:19 (Aug.) 1943.

Craigie examined microscopic sections of brain tissue from an African, an American and an Australian lungfish. In the African and American forms he found a large-meshed capillary network, less complex than in most other fishes. In the Australian fish, in addition to the network were capillaries in the form of hairpin loops. The presence of the latter indicates that the Australian form is the most primitive of the three.

ADDISON, Philadelphia.

VISUOMOTOR COORDINATION IN THE NEWT (TRITURUS VERIDESCENS) AFTER REGENERATION OF THE OPTIC NERVE. R. W. SPERRY, J. Comp. Neurol. **79**:33 (Aug.) 1943.

It has been shown by Stone that normal vision may be recovered in adult urodele amphibians after reimplantation and transplantation of adult eyes. Sperry has extended these observations in 58 adult newts by rotating the left eyeball 180 degrees on the optic axis, cutting the optic nerve and allowing regeneration. Tests of vision were made on the tenth day after operation and twice a week thereafter. The criteria of response used in judging vision included compensatory movements of the head to rotation of the visual field and visual localization of small moving objects. In the great majority of cases visual responses to photic stimulation of the left eye reappeared about thirty days after section of the left optic nerve. In all cases the recovered vision was systematically reversed and inverted, conforming to the rotated position of the retina. Although the reversal proved to be a great handicap to the animal's activities, it persisted without correction.

ADDISON, Philadelphia.

THE RETICULAR NATURE OF GLIA FIBERS IN THE CEREBRUM OF THE FROG AND IN THE HIGHER VERTEBRATES. WARREN ANDREW, J. Comp. Neurol. **79**:57 (Aug.) 1943.

Andrew studied the brains of 30 frogs, prepared by the methods of Ramón y Cajal, del Río Hortega and Penfield. For comparison, tissues of the human brain prepared by Cajal's gold chloride-mercury bichloride method were used. In the frog the glial framework was predominantly formed of processes of the ventricular ependymal cells. Different regions showed a varying manner of distribution of the ependymal processes. In some regions the fibers were seen as individual structures, running from the ependymal cells to the pia mater; in other regions they had fine branches which anastomosed and appeared to form a true reticulum. Study of the human cerebrum at high magnifications revealed very fine glial fibers which formed a continuous reticular framework. These observations, however, do not enable Andrew to decide whether the finest fibers should be considered always as the most delicate branchings of the astrocytes or as a general reticular framework on which the astrocytes lie.

ADDISON, Philadelphia.

CHROMATOLYSIS AND RECOVERY OF EFFERENT NEURONS. ROBERT STUART TURNER, J. Comp. Neurol. **79**:73 (Aug.) 1943.

Turner cut the right sciatic nerve of 20 guinea pigs just below the ischial tuberosity. The animals were allowed to live for varying lengths of time. From one-half these animals he removed the fifth lumbar segment of the spinal cord fifteen days after cutting the sciatic nerve, and from the other half he removed this segment at periods ranging from seven months to two years. The tissues were sectioned serially and stained with carbol thionin to show the cells. Total counts of normal and of chromatolyzed motor cells in the spinal cord were made on the side of operation and on the side of the intact nerve. As a control, Turner made counts of the total number of cells in the fifth lumbar segment of 13 guinea pigs not subjected to operation and found the two sides not significantly different. Fifteen days after section of the sciatic nerve on one side about 38 per cent of the anterior motor horn cells on the side of operation showed chromatolysis. The guinea pigs kept seven months to two years after section of the nerve showed about 16 per cent fewer anterior horn cells on the side of operation. It is deduced that recovery took place in approximately two thirds of the motor cells which had undergone definite chromatolysis.

ADDISON, Philadelphia.

AN EXPERIMENTAL STUDY OF THE FACIAL NERVE. JAMES O. FOLEY and FRANKLIN S. DUBOIS, J. Comp. Neurol. **79**:79 (Aug.) 1943.

Foley and DuBois have made a quantitative and qualitative analysis of the functional components in the rootlets, trunk and branches of the facial nerve. In

10 cats and 1 dog the somatic and visceral motor fibers were eliminated on the right side by sectioning the facial rootlets as they emerged from the pons or by a longitudinal cut of the pons in the region of the attached rootlets. After fourteen days both the right and the left facial nerve and their branches were dissected out, and specimens were taken from eight or more regions. These specimens were prepared with a silver technic to show fibers. In addition, in 1 cat the auricular nerve was sectioned as it emerged from the jugular ganglion, and in another cat a superior cervical ganglion was removed. A postoperative survival period of fourteen days was allowed these animals also, and the technic was the same as that employed with the others. For comparison, sections of the facial nerve of a cat not subjected to operation were stained for myelin. The somatic motor axons numbered on the average 9,000; the visceral motor axons, about 2,000, and the sensory fibers, 2,200. Of the visceral motor fibers, approximately 70 per cent were distributed in the great superficial petrosal nerve and 30 per cent in the chorda tympani. Of the sensory fibers, about 36 per cent passed into the great superficial petrosal nerve; 50 per cent entered the chorda tympani, and 14 per cent passed peripherally in the trunk of the facial nerve. Before emerging from the stylomastoid foramen, the facial nerve was joined by the auricular branch of the vagus nerve, which contained about 8,000 fibers. In the cat it appears that the few sensory fibers of the facial nerve which are distributed superficially to the head accompany the auricular branch of the vagus nerve.

ADDISON, Philadelphia.

EXTENSIVE UNILATERAL CEREBRAL REMOVALS IN THE PRIMATE: PHYSIOLOGIC EFFECTS AND RESULTANT DEGENERATION. FRED A. METTLER, J. Comp. Neurol. **79**:185 (Oct.) 1943.

Mettler studied 9 monkeys after making unilateral lesions of varying extent on the left hemisphere. From 3 of the animals he removed only portions of the cortex; from 1 animal he removed all the neocortex of the left cerebral hemisphere, and from 4 others, in addition to the cortex, he removed portions of the striate body. In the ninth animal the entire left hemisphere was removed as far as the posterior commissure. The activities of the animals were observed for varying periods, and finally histologic examinations were carried out. For each animal copious physiologic and histologic data are given, and a chart presenting data on the 7 principal subjects allows a quick comparison of important physiologic conditions, such as the patellar reflex, the plantar reflex, monomanual and bimanual feedings, posture of the right arm, direction of circling movements and resistance to passive movement. Mettler observes that in this series of progressively extensive unilateral cerebral removals there was gradual degradation of motor performance rather than paralysis. Spasticity was more conspicuous after combined cortical and subcortical damage than after cortical damage alone. Resistance to passive movement was first seen when the pallidum as well as the cortex was involved. From study of the sections of these brains, together with supplemental information from various other investigators, Mettler has constructed a series of thirty-six diagrams, which collectively present a working plan for the principal connections of the thalamic nuclei. Half these diagrams are the same as those in Mettler's "Neuroanatomy" (St. Louis, C. V. Mosby Company, 1943). Of the cortical fibers to the striatum, approximately one half come from the frontal cortex and the other half from the nonfrontal cortex. Only about one half of all the fibers from the frontal region originate in area 4. The compact part of the substantia nigra sends fibers to the pallidum, while the diffuse and lateral parts of the substantia nigra appear to discharge on the striatum. The pallidum receives fibers from the centromedian nucleus. This circuit appears responsible for some of the more complex patterns of associated movements.

ADDISON, Philadelphia.

Physiology and Biochemistry

OBSERVATIONS ON MUSCLE SPASM IN POLIOMYELITIS: ELECTROMYOGRAPHIC STUDIES ON EFFECT OF VARIOUS FORMS OF THERMAL THERAPY AND OF PROSTIGMINE. A. L. WATKINS and MARY A. B. BRAZIER, Arch. Phys. Therapy **26**:325 (June) 1945.

Hypersensitivity or spasm of muscles has been emphasized as one of the most characteristic aspects of the acute stage of poliomyelitis. Watkins and Brazier studied the influence of single applications of a therapeutic agent on muscle spasm during the first weeks of the disease. All patients were in the early infectious stage, and studies were restricted to adult patients. Six such patients were available for study. In all, 835 measurements were made, the first test usually being made within a few days after diagnosis had been established. Muscle spasm was measured by quantitation of the electrical discharges released on five seconds of passive stretching by known weights in order to test the effect of twenty minute applications of hot packs, infra-red radiation, luminous heat, short wave diathermy and the intramuscular injection of neostigmine (1.6 mg.) on this electrical component of spasm. Single applications of hot packs, infra-red radiation and diathermy had no effect. Luminous heat and neostigmine caused a decrease in spasm of approximately 25 per cent. This degree of change was not great enough to indicate a specific effect on spasm.

J. A. M. A.

Neuropathology

TUMORS OF THYMUS IN MYASTHENIA GRAVIS. N. A. MURRAY and J. R. MCDONALD, Am. J. Clin. Path. **15**:87 (March) 1945.

Murray and McDonald studied thymus glands removed from 10 fetuses and from 100 persons from the ages of 4 months to 86 years. They also studied thymomas associated with myasthenia gravis in 13 cases and thymic tumors removed surgically in 2 cases of myasthenia gravis. Several observations made by them suggested that these tumors are thymomas. Most primary tumors of the thymus associated with myasthenia gravis are of a single type. They are made up of lymphocytes and of larger pale cells with faintly acidophilic cytoplasm in varying proportions and indefinite cell boundaries. These tumors contain numerous small blood vessels and occasional Hassall corpuscles. A "lining up," or palisading, of the pale cells along connective tissue trabeculae and pseudorosette formation around blood vessels appear to be distinguishing features. If metastasis and direct extension are sufficient criteria for the diagnosis of malignancy, then these tumors are malignant. It is believed that "thymoma" is an adequate name for tumors of this type. The tumors which will metastasize cannot be distinguished from those which will not metastasize. The absence or presence of secondary germ centers (lymph follicles) does not point either to or away from malignancy. The

absence of differentiation of cortex and medulla is not a reliable criterion for the diagnosis of malignancy. The incidence of myasthenia gravis among patients with thymoma is nearly 100 per cent. Eaton has stated that the incidence of thymomas among patients with myasthenia gravis is 14 per cent. According to Bell, the incidence at necropsy of thymic dysplasia among patients who have died of myasthenia gravis is about 50 per cent.

J. A. M. A.

ALTERATIONS IN STRUCTURE OF MOTOR NERVE-ENDINGS IN SKELETAL MUSCLE OF RABBITS. WILLIAM B. DUBLIN, J. Nerv. & Ment. Dis. **100**:275 (Sept.) 1944.

By means of the gold chloride method, Dublin studied the structure of motor nerve endings in skeletal muscle of normal rabbits and in rabbits after curarization, hypothermia and exercise. There was considerable variation in the structure of the nerve endings in the untreated animals. No remarkable alteration was seen in the motor nerve endings of curarized muscle, although slight contraction of the endings was observed. After hypothermia induced by packing in ice rabbits lightly anesthetized with a barbiturate, there was no appreciable change in the motor nerve endings as studied in biopsy specimens. After exercise the motor nerve endings were observed to be expanded.

CHODOFF, Langley Field, Va.

A NEW METHOD FOR IMPREGNATION OF OLIGODENDROGLIA AND MICROGLIA IN ORDINARY NECROPSY MATERIAL. ANTONIA GRIÑO, J. Neuropath. & Exper. Neurol. **4**:93 (Jan.) 1945.

Griño describes a staining technic for the impregnation of oligodendroglia and microglia in specimens which have been subjected to the conditions of routine autopsy and fixed in solution of formaldehyde U. S. P. (1:4) from fifteen days to one year. The frozen sections are treated with an oxidizing agent and the cells impregnated with an ammoniacal solution of silver tungstate, followed by reduction in solution of formaldehyde U. S. P.

The author states that when this method is properly employed it is specific for oligodendroglia, microglia, their expansions and the adventitial cells of the vessels. Astrocytes and neurons are not brought out. Other organic and inorganic salts of silver (arsenate, molybdate, oxalate, citrate, etc.) were tried, without good results. Griño mentions the possibility that oligodendroglia and microglia may possess definite avidity for oxygen. No conclusions were drawn as to the mechanism of impregnation with silver compounds.

GUTTMAN, Philadelphia.

DEATH FROM ELECTRICAL CONVULSION THERAPY. F. J. NAPIER, J. Ment. Sc. **90**:875 (Oct.) 1944.

Napier describes 5 civilian deaths resulting from shock treatment. A sixth has been reported, but no details are available. These are the only known deaths from this cause in England and Wales since the treatment was started.

Of the 5, only 2 deaths resulted directly from the convulsion. Of these, 1 death was due to a hemorrhage involving both lobes of the thyroid gland and filling the mediastinum. Death occurred six hours after treatment, with only a little restlessness and ten minutes of dyspnea as a warning. This was the first shock treatment given the patient, who had had toxic diffuse goiter twenty-one years before but showed no abnormal physical signs on admission other than pallor. The other death directly attributable to shock was that of a 65 year old man with a blood pressure of 185 systolic and 90 diastolic, slight enlargement of the left ventricle and heart sounds of poor quality. Urinalysis revealed a specific gravity of 1.010, a trace of albumin and the presence of pus cells on one occasion. The patient was given five shocks without convulsion. The first, and last, convulsion resulted in acute collapse and death one-half hour later. There was pronounced relative preponderance of the left ventricle, and the myocardium was extremely soft.

Of the patients whose deaths did not directly follow shock, 1 fractured the acetabulum during the second treatment and died of pulmonary tuberculosis six months later. Another died in uremia after a fracture of the femur incurred during the third treatment. Another had bronchopneumonia six days after the second treatment and died four days later. Postmortem examination showed bronchopneumonia and chronic nephritis in the last 2 cases.

MCCARTER, Boston.

THE SPINAL FLUID IN HEINE-MEDIN DISEASE (ACUTE ANTERIOR POLIOMYELITIS). A. M. MARQUE, J. M. MACONE and C. R. GIÚDICE, Rev. neurol. de Buenos Aires **9**:248 (July-Sept.) 1944.

The authors report on the analysis of 129 specimens of spinal fluid taken in cases of anterior poliomyelitis during the epidemics of 1936 and 1942. The fluid was always clear, without xanthochromia, blood or spontaneous coagulation. The Pandy reaction was positive in 37 per cent of the specimens; it was usually negative in cases in which the illness was of less than fifteen days' duration. Pleocytosis, characteristic of all cases, was most pronounced during the first few days and in the week following the appearance of paralysis. No relation was observed between the intensity of the disease, the types of paralysis and the number of cells in the fluid. The highest number of cells was 600 per cubic millimeter, on the sixth day, in a boy of 5 years with paraplegia; the lowest number of cells was 6.4 cells per cubic millimeter, on the eighth day, in a girl of 2½ years with paraplegia. The cells gradually diminished in number. They were mainly lymphocytes, with polymorphonuclear leukocytes in some cases. The authors failed to observe the predominance of polymorphonuclear leukocytes during the first twenty-four to forty-eight hours, as reported by Peabody. An increase in protein content was observed in almost all cases, especially during defervescence and after paralysis set in; the amount varied from 50 to 200 mg. per hundred cubic centimeters. The sugar was usually increased, except in 1 case (34 mg. per hundred cubic centimeters). There were no significant changes in the chloride content, which varied from 640 to 819 mg. per hundred cubic centimeters. The colloidal gold curve was normal in 38 per cent of the cases; in 62 per cent the curves were atypical. The Guillain test was made in 32 cases, with precipitation in the second zone in most cases. The Wassermann reaction was negative in all cases.

SAVITSKY, New York.

SECONDARY EFFECTS OF QUINACRINE [ATABRINE] ON NERVOUS SYSTEM. H. VOLLMER and H. LIEBIG, Deutsche med. Wchnschr. **70**:415 (July 21) 1944.

Experiments on rabbits and cats revealed certain secondary effects of quinacrine on the central nervous

system of these animals. Psychosis and motor excitement were caused by suicidal attempts with large doses of quinacrine hydrochloride (1.9 to 9 Gm.). Vollmer and Liebig report 4 cases of recurrent tertian malaria in which secondary effects on the central nervous system were observed. The occurrence of these reactions was not in agreement with the observations of other authors, who have asserted that reactions of this type do not result from the administration of therapeutic doses of the drug. The incidence (4 in 450 cases) was low. Psychosis resulted in 3 cases from intramuscular injection of quinacrine, and psychosis associated with bulbar paralysis and flaccid paralysis of the lower extremities, in 1 case. The aforementioned disturbances were of short duration. There were no cases of irreversible effects.

J. A. M. A.

Psychiatry and Psychopathology

NEUROPSYCHIATRIC CASUALTIES FROM GAUDALCANAL: I. PERSISTENT SYMPTOMS IN THREE CASES. ALBERT A. ROSNER, Am. J. M. Sc. **207**:770 (June) 1944.

Rosner reports the cases of 3 typical American soldiers, 27, 23 and 20 years of age, respectively, with diverse sociologic and geographic origins. They were of normal emotional and psychologic makeup, with no family histories of mental disorder. Their fundamental patterns of reactivity had been considered normal in the past, but after the shattering experiences at Guadalcanal they manifested such grave behavior disturbances that they became unfit for military duty. Of interest was the fact that their symptoms and complaints were similar. For example, such expressions as "It's too much for me; I get nervous when I get out there and have to give orders; I can't do it" or "I feel weak and I have no energy," were typical of the conditions. All had been exposed to extreme exhaustion, fear, hunger, thirst, tropical heat and humidity, and jeopardy of life and limb. Although 2 of them had been rendered unconscious as a result of shell bursts, there were no postconcussion symptoms or amnesia. One year later symptoms still persisted despite active therapeutic measures.

MICHAELS, M.C., A.U.S.

UNUSUAL REACTIONS TO ELECTROSHOCK. CARROLL W. OSGOOD, J. Nerv. & Ment. Dis. **100**:343 (Oct.) 1944.

A survey was made of all unusual reactions of patients treated with electric shock in an attempt to answer questions as to the safety and effectiveness of this method of treatment. The reactions are divided into two groups: those which appear in the treatment room and those which present themselves as later reactions. It has been suggested that petit mal seizures, generally agreed to be ineffectual, may be harmful. No patients in the survey who were prone to petit mal attacks showed any ill effects, although they demonstrated rather less than average improvement. The panic reaction seems to be characteristic for a given patient, but it may be modified by medication before treatment. Repetitive speech lasting for an abnormal period, without apparent ill effect, was observed.

Among the later reactions are increased restlessness or agitation without much clouding, dazed retardation and states of excitement and uncooperativeness. These reactions, although occasionally alarming, had no untoward effects on the progress of the disease. The author believes that while patients may be made temporarily worse mentally, as well as being subjected to certain physical hazards, and while their psychoses may be activated or may progress in spite of treatment, they are seldom, if ever, made permanently worse.

CHODOFF, Langley Field, Va.

THE PROGNOSTIC VALUE OF CLINICAL FINDINGS IN CASES TREATED WITH ELECTRIC SHOCK. LEONARD GOLD and CARMELO J. CHIARELLO, J. Nerv. & Ment. Dis. **100**:577 (Dec.) 1944.

Gold and Chiarello studied the relation between the results of electric shock therapy and certain individual clinical observations in 121 consecutive male patients. Of the total, 20 per cent showed "much improvement," 22 per cent "improvement," 15 per cent "improved behavior" and 42 per cent no change. Indicative of a good prognosis prior to treatment was a symptom complex of muteness, perplexity and confusion, fear of an immediate personal threat or danger, and depression. Patients in the age groups of 11 to 20 and 51 to 60 years did better than those in the intervening period. Other favorable factors were duration of illness of less than one year, sudden onset, exogenic precipitating factors, good marital and sexual adjustments and a background of familial stability. Factors portending a poor prognosis were gradual onset, long duration of illness, previous shock therapy, gradual loss of interest, negativism, restlessness, ideas of reference and grandiose delusions. The authors believe that detailed examination of individual symptoms is more important in prognosis than the categorizing of patients into formal diagnostic groups.

CHODOFF, Langley Field, Va.

PEPTIC ULCERS IN THE INSANE. O. J. POLLAK and F. KREPLICK, J. Nerv. & Ment. Dis. **101**:1 (Jan.) 1945.

Pollak and Kreplick, in an analysis of the frequency with which peptic ulcer was observed in 2,000 necropsies performed on patients with mental disease from a state hospital, found an incidence of 2.1 per cent. No significant correlation was noted between the presence of peptic ulcer, on the one hand, and the type of insanity, the character of the mental symptoms or the sexual adjustment of the patient, on the other. More than one-half the patients displayed a prepsychotic mental makeup of the type commonly encountered in nonpsychotic patients with ulcer. No undue predominance of either the asthenic or the hypersthenic type of body build was found to be associated with the occurrence of ulcer. One third of the patients had multiple ulcers, as compared with the usually reported figure of 5 to 10 per cent. The incidence of ruptured ulcer in 13 patients (31 per cent) is explained partly on the basis of the visceral atony often present in psychotic patients. In 12 patients the ulcers proved fatal, although only a small number presented symptoms of ulcer during life.

CHODOFF, Langley Field, Va.

Meninges and Blood Vessels

A CASE OF ACUTE MENINGITIS CAUSED BY NEISSERIA PERFLAVA. LAWRENCE H. SOPHIAN, Am. J. M. Sc. **207**:376 (March) 1944.

Sophian reports the case of a 31 year old merchant seaman who was admitted in an acutely ill condition. He had hallucinations; tremor; a history of recent alcoholic intoxication; Babinski, Oppenheim and Gordon signs on the left side; a partial Babinski sign on the right side, and a Brudzinski sign bilaterally. There was extreme rigidity of the neck, and the Kernig sign

was positive. The patient responded only to painful stimuli.

A spinal tap showed an initial pressure of 220 cm. and a cell count of 15,000 leukocytes, mostly neutrophils, per cubic millimeter. The organisms found appeared larger than the usual strain of Neisseria intracellularis.

Autopsy revealed a very thick, greenish yellow exudate closely attached to the base of the brain, extending from the optic chiasm to the medulla. The thickest exudate was localized around the pituitary gland. Microscopic examination showed an unusually dense accumulation of neutrophils in the pia and arachnoid. The causative organism was found to be Neisseria perflava. The portal of entry, found at autopsy, was a congenital defect in the roof of the sphenoid sinus.

MICHAELS, M.C., A.U.S.

THE EVALUATION OF ALCOHOL LUMBAR PARAVERTEBRAL BLOCK IN PERIPHERAL VASCULAR DISEASE. GAMLIEL SALAND and CHARLES KLEIN, Am. J. M. Sc. **207**:749 (June) 1944.

Saland and Klein studied 16 patients who applied to the vascular clinic for relief of symptoms. The patients were treated by paravertebral block; temperature readings at the surface of the skin were taken one hour before injection to allow the temperature of the skin to stabilize. Follow-up temperature readings of the surface of the skin were made at various intervals during the first three days and subsequently at longer intervals. A difference in temperature of 2 C. in corresponding areas of the extremities was considered significant. Five patients showed complete immediate vasodilatation, lasting three to one hundred and eight days; 9 patients showed an immediate or delayed significant vasodilatation, lasting three days to two years. Neuritis was produced when a larger amount of alcohol was injected. In no instance did the neuritis last longer than forty-five days. Of 10 of the 12 patients with peripheral vascular disease, 5 showed improvement, three showed no change and 2 were definitely worse. There was no correlation between claudication time and the degree of vasodilatation.

MICHAELS, M.C., A.U.S.

SALMONELLA CHOLERAE SUIS MENINGITIS. ERWIN R. NETER, Arch. Int. Med. **73**:425 (May) 1944.

Neter reports the case of a white girl aged 3 years and 11 months who was blind and hydrocephalic. Bacteremia and meningitis developed. Cultures of the blood and the cerebrospinal fluid revealed the presence of many gram-negative bacilli, which were identified as Salmonella cholerae suis (Salmonella suipestifer). Examination of the feces failed to reveal paratyphoid bacilli. The serum of the patient failed to show the presence of specific agglutinins. Sulfadiazine therapy was instituted, but in spite of this treatment the child died the following day. Cultures of the stools of the child's father, mother and brother failed to show evidence of paratyphoid bacilli, and agglutinins against the patient's strain could not be demonstrated in their serum.

The author reviews 78 cases of Salmonella meningitis described during the past twenty years. Twelve different species and types of Salmonella have been encountered in the past as the causative agent. These represent only a fraction of the species known to be pathogenic to man. Not a single case of meningitis due to the paratyphoid A bacillus is included in the group. Members of group B of the genus Salmonella account for 26, or one third, of all cases. Only 5 cases of meningitis were caused by Salmonella cholerae suis, the sole representative of group C—more than one half of all instances of Salmonella meningitis were due to members of group D. Group E is represented by Salmonella sp. (London type) in a single case.

The author concludes that the prognosis of Salmonella meningitis is poor, but a few cases with recovery have been reported. No conclusions with respect to the efficacy of sulfonamide compounds can as yet be drawn, and they are not equally effective toward all species and types of the genus Salmonella.

GUTTMAN, Philadelphia.

THROMBOPHLEBITIS OF A CAVERNOUS SINUS FOLLOWING EXTRACTION OF TEETH. IRVING H. WIESENFELD and EDWARD PHILLIPS, Arch. Otolaryng. **40**:497 (Dec.) 1944.

Wiesenfeld and Phillips report a case of thrombophlebitis of the cavernous sinus in which recovery followed treatment with penicillin and heparin. The patient, an 18 year old white youth, had bilateral maxillary sinusitis. Conservative treatment was advised; but when pain developed in the upper teeth on the right side, a dentist extracted the right upper first bicuspid, as well as a supernumerary tooth which lay alongside the bicuspid and which was impacted in the hard palate. The extraction was performed with difficulty. The patient was next seen two days after the extraction, when he appeared acutely ill. Cellulitis of the right cheek was obvious, and the temperature was 102 F. Sulfadiazine treatment was begun. Two days later the patient was hospitalized, and cultures of the pus from the draining tooth socket revealed Staphylococcus aureus. The dose of sulfadiazine was increased until the level of the drug in the blood ranged from 9.6 to 12.8 mg. per hundred cubic centimeters. In spite of this, the infection spread, and one week later a diagnosis of thrombophlebitis of the right cavernous sinus was established. There was palsy of all the extraocular muscles on that side, and the disk was found to be choked to 8 D. Several hours later proptosis of the left eye developed, and 4 D. of papilledema was present. The patient seemed moribund, when penicillin therapy was instituted. A continuous intravenous drip of penicillin and heparin was started and continued for eleven days. The dosage of heparin was adjusted to maintain the clotting time at approximately fifteen minutes. A total dose of 2,000,000 units of penicillin was given in twenty days, the drug being administered intramuscularly during the last nine days.

The case is illustrative of the well known dangers of operation on oral structures in the presence of acute infection. It is assumed that the staphylococcic infection was refractory to the sulfadiazine and that recovery of the patient was due to penicillin. The role of heparin in the recovery is difficult to evaluate.

RYAN, Philadelphia.

MENINGOENCEPHALITIS IN LYMPHOGRANULOMA VENEREUM. CHRIS J. D. ZARAFONETIS, New England J. Med. **230**:567 (May 11) 1944.

Zarafonetis reports on 2 patients with lymphogranuloma venereum. Both had complaints of headache, and 1 had a five day period of amnesia followed by confusion for about seven days. Manometric studies revealed a persistent block of the subarachnoid space. Both patients gave positive reactions to complement fixation tests and the Frei test, and a virus was isolated

from an inguinal lymph node of 1 patient five months after the onset of his illness. The observations on these patients indicate that lymphogranuloma venereum may produce meningoencephalitis, as well as myelomeningoencephalitis with adhesive arachnoiditis.

GUTTMAN, Philadelphia.

MENINGOGENIC REFLEX MYRINGITIS. FELIPE CORA ELISEHT and JUAN MONTERO, Prensa méd. argent. **31**:2652 (Dec. 27) 1944.

In October 1944, a paper on "reflex myringitis" of meningeal origin by Marinho appeared in a Brazilian journal. Marinho stated that this was an early sign of meningeal irritation in nonotogenic involvement of the meninges. Ferrari had described hyperemia of the tympanic membrane as an early sign of tuberculous meningitis. Marinho described the sign as a reddening of the tympanic membrane with an intact cone of light and no blurring of the landmarks. In occasional cases the congestion becomes so marked as to cause blurring of the anatomic landmarks. The authors state that they looked for this sign described by Marinho in cases of nonotogenic meningitis, hemorrhagic pachymeningitis and head traumas, but they were unable to find it. They indicate the difficulty in ruling out infections of the middle ear as the cause of the changes in the tympanic membrane.

SAVITSKY, New York.

MENINGEAL APOPLEXY. A. FORTES, Rev. mex. de psiquiat., neurol. y med. leg. **9**:17 (Jan.) 1945.

Fortes reports 2 cases of subarachnoid hemorrhage. The first was that of a 36 year old white man whose illness began with sudden, intense frontal headache, followed by loss of consciousness. Right hemiplegia was found on his admission to the hospital. The author does not mention meningeal signs. The patient was in a stupor. The right internal carotid artery was ligated, and a trephination was done in the left temporal region; 20 cc. of blood was aspirated. After the operation the hemiplegia disappeared. As the patient recovered from stupor, aphasia, agraphia and alexia developed. Three months after the operation he had an epileptic attack and showed a mild residual aphasic defect.

The other case was that of a 40 year old white woman whose illness also began with sudden, severe pain in the head and transitory loss of consciousness, preceded for a short time by paraesthesias in all the limbs. On admission to the hospital, the patient showed generalized increase in the tendon reflexes. No signs of meningeal irritation are mentioned. The right internal carotid artery was ligated. The pain disappeared, and the patient's condition cleared up fourteen days after the operation.

SAVITSKY, New York.

Diseases of the Spinal Cord

X-RAYS IN DIAGNOSIS OF POSTERIOR HERNIATION OF INTERVERTEBRAL DISK. A. E. CHILDE, Canad. M. A. J. **52**:458 (May) 1945.

At the Montreal Neurological Institute and at the No. 1 Canadian Neurological Hospital various methods have been used to diagnose herniation of the intervertebral disks. Since early in 1942 the injection of iodized oil, with subsequent aspiration, has become routine. During part of this period iodized poppyseed oil has been the medium, but Pantopaque is much to be preferred, not only because it is much more easily injected and aspirated but because it moves more freely. There is the additional advantage that any small amount which may be left in place is gradually spontaneously absorbed. While it is not as radiopaque as iodized poppyseed oil, it is sufficiently dense for practical purposes. Childe stresses that plain roentgenograms should always be made first. These films usually are not diagnostic of such a herniation but may offer suggestive evidence, and they help to exclude other lesions. Myelographic examination when properly performed using Pantopaque with subsequent aspiration is an accurate and safe method. Multiple herniations of the disks are not uncommon, and many unsatisfactory results may be explained on this basis if operation is undertaken without previous myelographic studies. Herniation of sufficient size to produce great disability may cause only comparatively small deformities of the subarachnoid space. Hence the use of a relatively large quantity of oil is advisable, and multiple spot films should be made routinely to avoid missing minor deformities not readily seen under the fluoroscope. Myelographic study reveals that the size of some herniations undergoes change, owing to such factors as weight bearing, traction, muscular activity, flexion and extension. Herniated intervertebral disks in the cervical region are often complicated by hypertrophic bone formation. Tumors in the lumbar and sacral regions, and occasionally in the cervical region, may produce signs and symptoms which are clinically indistinguishable from those produced by herniated intervertebral disk. Myelographic examination will usually differentiate between a tumor and a herniated disk.

J. A. M. A.

Peripheral and Cranial Nerves

TOTAL HERPES ZOSTER OF THE OPHTHALMIC, MAXILLARY AND MANDIBULAR DIVISIONS OF THE TRIGEMINAL NERVE. HUGH O'NEILL, Arch. Ophth. **33**:237 (March) 1945.

Herpes zoster ophthalmicus, or herpes zoster of the gasserian ganglion, is rare. Indeed, it is so rare that Rice stated that no cases of ophthalmic herpes zoster were mentioned, for example, in the report of one of the largest ophthalmologic and otologic hospitals in the United States, in which over 100,000 patients with ocular disease were treated in 1922. On the other hand, Gundersen, in searching for cases of herpes zoster ophthalmicus, found 10 per annum at the Massachusetts Eye and Ear Infirmary, in Boston, over a five year period.

Herpes zoster involving the ophthalmic, maxillary and mandibular divisions of the fifth cranial nerve is rare, judged by the absence of reported cases in the literature. Herpes zoster of the trigeminal nerve with concomitant cutaneous involvement of the geniculate ganglion, the combination of which likewise has not been reported in the literature, is rare indeed, although Fuchs, cited by Graves, reported 2 cases in which with herpes zoster ophthalmicus there was concurrent involvement of the seventh cranial nerve, with resulting lagophthalmos and keratitis. This combination is not rare, nor is that of herpes zoster ophthalmicus with involvement of the third, fourth, sixth and seventh cranial nerves, with ocular palsy.

O'Neill reported a case of partial herpes zoster of the seventh cranial nerve, involvement of the vestibular ganglion of the eighth cranial nerve and complete herpes zoster involving all three divisions of the trigeminal nerve. On account of the severe pain, the ocular involvement and the residual scarring on the cutaneous

branches of the trigeminal nerve, a diagnosis of herpes simplex or of herpes febrilis was inadmissible. The ocular signs included optic neuritis, exophthalmos, keratitis profunda and probable mild involvement of the third, fourth and sixth cranial nerves. No evidence for classifying this case as one of symptomatic herpes zoster arising from encephalitis, syphilis, tuberculosis, leukemia, Hodgkin's disease, hemorrhage in the cerebellopontile angle or cerebral tumor was found. On the other hand, in view of the severe pain and the cutaneous herpetiform manifestations, the case was obviously one of idiopathic herpes zoster of the fifth (complete), seventh (partial) and eighth (vestibular) cranial nerves.

SPAETH, Philadelphia.

UNUSUAL RAPID EVOLUTION IN GUILLAIN-BARRÉ SYNDROME WITH BULBAR PALSY. AUTHUR A. BRISKIER, J. Nerv. & Ment. Dis. **100**:462 (Nov.) 1944.

Briskier reports a case of the Guillain-Barré syndrome in a 40 year old man with a fatal termination eighteen hours after his admission to the hospital. Unusual features of the case were the very rapid evolution and the widespread involvement of the central nervous system. No causative organism was identified.

CHODOFF, Langley Field, Va.

RETROBULBAR OPTIC NEURITIS. R. A. GREEVES, Lancet **1**:715 (June 3) 1944.

Greeves lists three signs and symptoms associated with acute retrobulbar optic neuritis besides the central scotoma. These are: (1) partial dilatation of the pupil, which reacts to light but does not hold the reaction; (2) a sensation of pain when the eyeball is moved, and (3) tenderness of the globe to pressure. He feels that the last is found usually only with pressure on the upper surface of the eyeball and is sensed by the patient as though in the midline of that structure. The pupillary reaction described is the most frequently found of the three, but even this may be absent or anomalous.

MCCARTER, Boston.

Treatment, Neurosurgery

RAPID TREATMENT OF NEUROSYPHILIS WITH MALARIA AND CHEMOTHERAPY. BERNHARD DATTNER, EVAN W. THOMAS and GERTRUDE WEXLER, Am. J. Syph., Gonor. & Ven. Dis. **28**:265 (May) 1944.

Dattner, Thomas and Wexler report their experiences in treating patients with acute neurosyphilis. The clinical material consisted of 419 patients with neurosyphilis who were treated with malaria followed by antisyphilitic chemotherapy. Five of the patients were retreated with a different strain of malaria. Of 424 courses of malarial therapy, 148 consisted of eight paroxysms followed by routine chemotherapy and 276 of eight paroxysms followed by administration of oxyphenarsine hydrochloride, 0.06 Gm. each day, for ten days. Of the 419 patients (424 treatment courses), 10 died; 62 could not be reached for follow-up observation, and 54 were too recently treated for evaluation of the effects of therapy. Therefore, data on the results of therapy are limited to 293 patients, or 298 treatment courses. The follow-up study included observations on 82 per cent of all patients, and the follow-up period extended from six to forty-eight months after the cessation of treatment.

The authors could not observe any significant difference in the therapeutic results in the two groups. They state that satisfactory results, as shown by examination of the cerebrospinal fluid, were obtained in 85.9 per cent of the patients.

Dattner, Thomas and Wexler stress the fact that the increase in cells and protein in the cerebrospinal fluid, in addition to a positive Wassermann reaction, furnishes the best guide to selection of patients for effective fever therapy. The authors conclude that "when the spinal fluid findings are used as a guide, prolonged chemotherapy following malaria is considered unnecessary and unwise."

GUTTMAN, Philadelphia.

SENSITIZATION TO THIAMINE HYDROCHLORIDE. WILLIAM STEIN and MATES MORGENSTERN, Ann. Int. Med. **20**:862 (May) 1944.

Stein and Morgenstern report the case history of a man who was addicted to alcohol and who had an entirely negative history for allergy. He received seven injections of thiamine hydrochloride (15,000 to 20,000 international [U. S. P.] units) during a four month period. Approximately fifteen minutes after each treatment he suffered from severe pruritis and a large reddened wheal at the site of the injection. These phenomena persisted for several hours. About one month after the seventh injection the patient received 30,000 international units of thiamine hydrochloride by vein. About thirty seconds later the patient experienced local, and then generalized, pruritis. He became weak, cold and clammy, very dyspneic, cyanotic and eventually unconscious. The pulse was rapid and thready. Epinephrine hydrochloride (1:1,000), 0.3 cc., and caffeine and sodium benzoate, 0.5 Gm., were given subcutaneously. About three hours later the reaction had almost completely subsided, and the following day the patient had completely recovered. About forty-eight hours after this episode the patient exhibited a positive reaction by intradermal test with the original solution of thiamine hydrochloride.

The authors report the case as the third recorded instance of sensitization to thiamine hydrochloride. They conclude that intradermal testing with thiamine hydrochloride is advisable, prior to its parenteral administration, particularly when the patient has previously received parenteral thiamine hydrochloride.

GUTTMAN, Philadelphia.

SUDDEN "EXHAUSTIVE" DEATH IN EXCITED PATIENTS. N. R. SHULACK, Psychiatric Quart. **18**:3 (Jan.) 1944.

Shulack discusses mechanisms of sudden exhaustive death in excited patients. He points out that such death may come very quickly and may be expected in hyperactive patients in the presence of a rapid, thready pulse, profuse perspiration and increasing hyperpyrexia. He postulates that in these patients there is marked peripheral vasodilatation and a positive potassium balance. Treatment consists in the following measures: (1) maintenance of nourishment, body glucose and water to replace that lost from perspiration, through tubal feedings, rectal drip, veniclysis and hypodermoclysis; (2) subnarcosis (barbiturates, paraldehyde) to reduce general toxemia due to exhausting metabolic products; (3) replacement of sodium (oral or parenteral administration of sodium chloride), (4) low potassium diet, and (5) repeated intravenous administration of adrenal cortex extract (desoxycorticosterone acetate) or Escahatin

(adrenal cortex extract) in doses of 1 cc. three times a day until the condition begins to improve, and a daily single dose until the patient is out of danger of exhaustion.

Four cases are described: The 2 patients who did not receive large doses of sodium chloride and adrenal cortex extract died, and the 2 who received sodium chloride desoxycorticosterone acetate or Eschatin lived.

McCarter, Boston.

Use of Metrazol in Barbiturate Poisoning. Serge Androp, Psychiatric Quart. **18**:13 (Jan.) 1944.

Androp discusses the various analeptics used in treatment of barbiturate poisoning: picrotoxin, metrazol, ephedrine and strychnine. The first two drugs are the most important because the most efficacious. Picrotoxin acts more slowly, and its effect is more prolonged. But since the effect is cumulative, there is the danger that the dose given for an immediate therapeutic effect may later cause convulsions. Metrazol acts quickly and to a maximum degree at once. Both drugs have a selective stimulating action on the centers depressed by the barbiturates, particularly the respiratory center.

The author reports the case of a 36 year old man with catatonia who rushed into the ward office, snatched a bottle of sodium amytal from the nurse and swallowed all its contents (102 grains [7.2 Gm.]). He was treated with intravenous injections of metrazol, 36 cc. being given in divided doses over the next six hours. He recovered, without untoward results. Elimination of the amytal was aided by high enemas and intravenous injections of dextrose and saline solution.

The author warns that one must keep an ever-watchful attitude in cases of catatonic schizophrenia. In spite of the seeming oblivion, catatonic patients do receive impressions of events and life about them, as attested recently by patients after shock therapy. It is also suggested that no more sedatives and hypnotics be kept in the ward than is necessary for daily consumption.

McCarter, Boston.

Sleep-Electro-Shock Therapy. H. S. Rubinstein, Science **101**:430 (April 27) 1945.

Rubinstein reports on the administration of an aqueous solution of pentothal sodium prior to electric shock therapy, which can be given while the patient is asleep. This method can be used in treatment of patients who refuse to continue with the therapy because of fear and persons for whom psychomotor excitability, as manifested by excitement, agitation, restlessness, shouting and combativeness, is undesirable.

Guttman, Philadelphia.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY AND CHICAGO NEUROLOGICAL SOCIETY

DAVID SLIGHT, M.B., *Presiding*

Joint Meeting, Jan. 6, 1945

Aleutian Paradox: Psychoneurotic Malingering. COMDR. A. R. MACLEAN (MC), U.S.N.R.

War Neuroses. LIEUT. COMDR. L. A. SCHWARTZ (MC), U.S.N.R.

What is a war neurosis? All are agreed that the usual psychoneuroses encountered in peacetime should not be termed war neuroses simply because they occur in a war setting. When these conditions are excluded, a group of cases is left in which the disturbance does not conform entirely to the nosologic criteria of psychoneuroses and which can be classified as such only with some difficulty. It is this group of cases in which I am interested, cases actually presenting a question of psychoneurotic symptoms in previously stable persons more than one of true psychoneuroses. One is confronted at once with the problem of what to call this disturbance and how to delineate clearly the syndrome variously called "war neurosis," "traumatic neurosis" and, of late, "combat fatigue."

The characteristic symptom of the "traumatic neurosis" is undoubtedly the "repetitious catastrophic nightmare." In its absence the diagnosis is suspect. Closely following the nightmare in frequency is the "startle reaction," produced by sudden loud noises and accompanied with physiologic evidence of anxiety, tremor, dilated pupils, sweating, dry mouth, flushing or pallor, palpitation and, in acute conditions, actual panic. Accompanying these symptoms are "a subtle personality change" which at times suggests the facies of schizophrenia and a guilt reaction with emotional depression.

There are, therefore, four arbitrary criteria for the diagnosis of "war neurosis," or "combat fatigue": first, a stable personality prior to the appearance of the traumatically determined emotional disturbance; second, combat experience of sufficient intensity to render it feasible as a precipitating agent; third, objective evidence of subjective anxiety, and, fourth, recoverability.

As an etiologic factor in the "traumatic neurosis," the personality is chiefly of importance in determining the severity of the neurotic symptoms under a given stimulus. In this connection, one finds two personality types —the emotionally and intellectually immature person, and the fully matured, independent older man—which appear to be of greatest importance in predisposition and which suggest a poor prognosis. Of more direct importance in the production of symptoms is the setting of interpersonal relationships in which the traumatic event occurs. In the patient's own story of the precipitation of the neurosis, four factors have occurred, singly or grouped, in too great frequency to be ignored: first, his having entered combat without faith and confidence in his leader; second, his having been insufficiently trained; third, his having entered combat surrounded by new shipmates, whose conduct under fire he had not had time to estimate, and fourth, his having experienced the combat situation when he was suffering with great physical fatigue.

It is believed that these four factors can be controlled to some extent and thus utilized in the prevention of "war neurosis" or "combat fatigue." Two other observations concerning the etiologic factors are of special therapeutic importance: 1. The difficulty in returning a patient to combat duty is increased in direct proportion to the distance to the front from which the patient has been evacuated. 2. All symptoms are liable to aggravation in the presence of loved ones, friends, relatives, spouse and family.

The preventive treatment of combat fatigue has been clearly indicated in the foregoing discussion. Active therapy consists in rest and emotional desensitization. Men should be given a certain period in which to "digest" the emotional turmoil of one traumatic experience before being exposed to another. This is best accomplished in a center where directed recreation and physical work are available, and not in the overprotected, emotionally charged atmosphere of their homes, which they meet on survivors' leave.

Those who have suffered from uncomplicated combat fatigue and who have recovered with two to three months of treatment or less are good material for retention in the service. As a rule, they should be returned to the duty they feel capable of handling. Symptoms of conversion hysteria and anxiety, not connected with startle, are bad omens. These men, with war neuroses, will eventually reach hospitals in the United States, where they will be found unresponsive to treatment until their discharge from the Naval service is assured. Their discharge need not await recovery; frequently the survey board is the therapeutic agent necessary to initiate recovery. Under governmental organization, the Veterans Administration is charged with the rehabilitation of these men.

DISCUSSION ON PAPERS BY COMMANDERS MACLEAN AND SCHWARTZ

MAJOR NORMAN LEVY: Evidently, the Aleutians, although the men see little combat except for bombing operations, present essentially the same problem of malingering as that met with in the combat personnel of the Air Forces in North Africa and Italy. My colleagues and I learned quickly that there was little practical point in attempting to differentiate neurotic reactions and malingering. The psychodynamic basis is essentially the same. The two conditions differ clinically, however. With regard to men who under the stresses of modern warfare or combat flying begin to exhibit emotional difficulties, it does not matter, from the practical point of view, whether the disabling symptoms are largely on a conscious level or are entirely on an unconscious level. The important thing is that the man is having difficulty in adjusting to the combat situation, and this condition has to be handled immediately. There is no value in distinguishing between the two. The fundamental problem, the patient's anxiety and fear in relation to the combat situation, must be attacked and therapy directed toward that rather than toward the symptoms themselves. In that way, in a large percentage of cases, one can help the combat personnel, and in many instances one can keep them continually in combat. Our experience has been exactly the same as Commander MacLean's. The men rise to whatever level is set for them, within certain limits. If one sets a relatively low level of performance by having medical officers who are overprotective and indulgent and who do not expect enough from the men in the way of self sacrifice in regard to functional symptoms, then one may have on one's hands an epidemic of these functional

symptoms. The medical officer has to be an authoritative person, who will refuse to allow men to get out of combat because of mild to moderately severe functional symptoms. That sounds, I'm sure, cruel and tough, but it is essential in the management of combat personnel who do not want to stay in combat. We had this problem with our flight surgeons. Our flight surgeons had been taught in this country that when men manifest nervous symptoms they must be grounded. In the new groups which came over, our first problem was to reorient our flight surgeons and get them to see that they had to be tough with the men and not ground them, because if they did there would be a tremendous increase in the number of men who have functional symptoms, especially conscious exaggerations of minor difficulties. As Commander MacLean found, we had to demand a good deal of self sacrifice from the men, and then they would rise to that level. If we let down the bars, they would not rise to whatever level we set for them.

LIEUT. COMDR. A. R. MACLEAN: Many of the things presented in my paper I have learned through the experience of other medical men who were in the service before me. They taught me the things I had to know to function as a Naval medical officer; as Major Levy, from the Mediterranean, so aptly described it, my levels had to be raised. I think that the level of psychiatry throughout the nation will have to be raised, so that the old theory of the life function of reward and punishment does not do a serious disservice to men discharged from the military service as psychoneurotic. Lifelong pensions as a reward solely for the effort made while in the Army should be considered, from our point of view, with disparagement.

DR. RALPH HAMILL, Chicago: I spent this morning at Hines Hospital, where I have spent up to six mornings a month for the past twenty-five years. As long as the Veterans Bureau is handling the problem of neurosis, there will be tremendous questions to be decided in relation to the future, if one takes into consideration what is likely to happen in the political situation, because of activity of the American Legion, for example. Any man who was discharged as neurotic at the time of World War I can now tell me any kind of story about not sleeping, his food not agreeing with him or of not being able to hold a job, and because he was discharged as neurotic in that war this condition is now service connected. Obviously, during the period of the depression money was very important; hence, one is faced with the need of considering what will happen in the next ten or fifteen years to the men in the present war whose disorders are called neuroses and are diagnosed as such. How are they going to use that diagnosis ten or fifteen years from now? Perhaps that does not apply to a great percentage of men at present, but they are the headaches of the Veterans Bureau.

ILLINOIS PSYCHIATRIC SOCIETY

DAVID SLIGHT, M.B., *Presiding*

Regular Meeting, Feb. 1, 1945

The Conditioned Reflex Treatment of Alcoholism.

DR. JOSEF A. KINDWALL and DR. L. H. ZIEGLER, Wauwatosa, Wis.

Experience based on 29 cases was reported, but only 3 cases were described. In 1 case, that of a woman, a strong aversion to alcohol was established, but a relapse into drinking occurred because of an extreme need of the effect of alcohol in an inadequate personality returned, with eagerness, for more conditioned reflex treatment. Barbiturates were substituted by the patient for alcohol, with a resulting toxic psychosis. Finally, she has achieved abstinence after the establishment of renewed association with Alcoholics Anonymous, Inc. (up to the time of this report) and lightened responsibilities at home.

In another case, that of a sales executive, there existed a profound underlying psychoneurosis and a pronounced deviation toward femininity, for which he unconsciously overcompensated. In his case there was an exceptionally high degree of aversion, which persisted through a series of electric shock treatments (with resultant profound confusion) given for his insomnia and tension. He was quite unable to drink liquor, though he tried in his confused phase to do so; and, though still tense and restless, he is sure that liquor will never tempt him again. In another case, that of a woman (not described in detail), the original aversion, not very strong, was further weakened by electric shock therapy, and a new series of conditioned reflex treatments failed to establish an aversion even as strong as the previous one.

The third case reported was that of a man, an executive, whose drinking had harmed him physically and who appeared dull and mentally slow on his admission to the hospital. No particular emotional problems could be found; he was a "good fellow," who had gradually become extremely alcoholic. He achieved a strong aversion to alcohol, took all the reenforcements, improved physically and, especially, mentally to a remarkable degree and has not had a relapse. He is greatly pleased with himself.

Apparently, the treatment can be helpful even if relapse does occur; patients often come back for further treatment.

The conditioned reflex—the actual aversion—is not necessarily the only valuable factor in the treatment. There are other factors, perhaps such as sacrifice, pride and emotional release, which may have an important bearing on results. The importance of follow-up observation was stressed, not only to insure adequate reenforcing treatments, but to maintain a favorable rapport between physician and patient. The authors feel that the method is a useful part of the total therapeutic armamentarium in the attack on alcoholism. The patients represented a great variety of types and of responses to the conditioned reflex treatment. More than half the patients have done well so far; the men have done better than the women.

DISCUSSION

DR. JULES H. MASSERMAN, Chicago: Dr. Kindwall requested that I devote my discussion to the possible theoretic and experimental background for his observations on alcoholism. I can do so briefly, especially since I presented a motion picture of some of my work on this problem before the society last year (in discussion on Edlin, J. V., and others: The Conditioned Aversion Treatment of Chronic Alcoholism, ARCH. NEUROL. & PSYCHIAT. **53**:86 [Jan.] 1945). It may be recalled that the rationale of the experiments was quite simple. An animal was trained to secure food on various signals by increasingly more complicated adaptive patterns: For instance, it had to open a box, to pass barriers and, finally, to work a switch in various difficult positions. If the animal was then given alcohol, the most complex and finely tuned adaptive patterns disappeared first, leaving only the simplest feeding responses. Conversely, as the effects of the drug wore off, the more complex patterns returned, in the order

in which they were originally learned, until the full adaptive capacities of the animal were again being used. After these control observations, the animal was subjected to a strong motivation conflict, such as that between hunger and fear, and acquired an experimental neurosis, characterized by evidences of anxiety, startle reactions, phobias, compulsions, severe inhibitions and "character" changes. If, now, the animal was again given alcohol, these most recent and most complex behavioral expressions of internal conflicts again disappeared in part, with the result that the animal reverted to similar feeding responses and so attained relief from tension and some goal satisfaction while under the influence of the drug. Finally, 11 of the 21 animals which repeatedly experienced this apparent relief from neurosis under the effect of alcohol began to prefer the drug in spontaneous choices and so appeared to become alcohol addicts; significantly, too, this addiction abated as their neurosis was relieved by various other therapeutic means. Perhaps it is relevant to mention an even more recent series of experiments, in which 9 animals were given alcohol before being submitted to motivational conflicts. The results to date indicate that here, too, the drug acts to diminish the traumatic effects of such situations and partly protects the animals from a resultant neurosis. I shall not take time to describe these experiments further, but their parallelism to the very human habit of taking "a couple of shots for a bracer" before undertaking an emotionally disturbing task deserves passing comment. Finally, it may be well to mention that other experiments with the barbiturates and with morphine indicate that these drugs, too, have effects similar to those of alcohol. Here, possibly, one has a clue to the reason that alcohol, the barbiturates and the opiates are the three most common forms of addiction among neurotic patients.

Now, as to the relevancy of these experiments and formulations to the clinical observations of Dr. Kindwall and Dr. Ziegler: The authors correctly point out that alcoholism is the expression of a neurotic need for a nepenthic and hypnotic drug which obliterates the poignancy of the neurotic person's perception of a world which he considers harassing and emotionally unbearable; he must, then, take alcohol to dull these perceptions and ameliorate the internal conflicts to which they give rise. Significantly, too, it is not alcohol itself that is craved; rather, it is psychologic effects—a point well illustrated by the woman patient who shifted from alcohol to the barbiturates when the former was not obtainable. In this connection, then, one must consider the pharmacologic action of alcohol, not merely the satisfactions of symbolic oral needs through drinking, which have perhaps been overstressed in psychoanalytic formulations. Drs. Kindwall and Ziegler also observed that if relief is not obtained through alcoholism internal emotional tensions may find expressions in other psychosomatic symptoms, such as the increased hypertension in 1 of their cases. Again, it must be recognized that alcohol, as shown by the work of Bender and many others, has a temporary toxic or permanently destructive effect on the cerebral cortex; it is, then, perhaps even more dangerous than usual to treat alcoholic addicts with shock therapy, since there is a possibility of decorticating to an unfortunate degree some of these otherwise intelligent, capable and socially useful alcohol addicts.

Lastly, one more point is perhaps worthy of discussion by the society, namely, the danger of overpublicizing this so-called conditioned reflex treatment to the point at which the public believes that there is now a new panacea for alcoholism—a fantasy which, I am sure, no psychiatrist accepts. Let me quote in this connection part of a letter I received only this morning from a woman in some remote hamlet in Virginia, who writes as follows: "I saw an article about your work in the local Sunday paper. I have a son who has taken to drink quite a lot. I have heard that there is a medicine which can be put in coffee that will put him against whiskey that maybe I can give him for his meals. Please send it to me immediately." One finds it hard to smile at such a pathetic appeal; but it is up to psychiatrists to educate the public as to the neurotic nature of alcoholism and the necessity of treating it by psychiatric means, and not by pharmacologic magic.

DR. MAX GITELSON, Chicago: I have often wondered, in connection with this method of treating alcoholism, whether the conditioning is through the drug itself or through the total situation in which the drug is given. Before one goes much further in discussing specific effects produced by the giving of the drug it would seem advisable to differentiate between the conditioning to the drug and the conditioning to the total situation, including the psychiatrist, the hospital and everything else concerned with the conditioning, both positive and negative.

I should like to raise the question whether it would be possible to treat some of these alcoholic patients by first conditioning them to the nauseating effect of the conditioning drug and subsequently giving them alcohol intravenously without their knowledge? Would this technic serve to differentiate the gross psychologic conditioning, which I have previously suggested may occur, from physiologic conditioning to the drug used in the treatment?

DR. MEYER SOLOMON, Chicago: In the use of the so-called conditioned reflex treatment, is it not true that a few preliminary conditions must be present? The patient's desire to get well is a determining factor, as well as his personality makeup and his willingness to spend time and money in the treatment. Is it not a fact that one must have the patient's faith and confidence that something can be done? Otherwise, the prognosis is not good. Also, should not the patient's personal problems be gone into? Perhaps his ambitions will have to be brought down to a more sensible level. It may be that his daily routine is too heavy, that he needs more recreational and social outlets or that a change in the kind of companions is desirable. In other words, the so-called conditioned reflex treatment is just a part of the general technic, in which all kinds of psychologic factors are considered as well as the general personality of the patient.

DR. CHARLES F. READ, Elgin, Ill.: With regard to the reenforcing aversion treatments that are carried on at various intervals after the primary ones have been completed, has any attempt been made to conduct them with the patient under hypnosis, without the use of alcohol? Since the patients often come back for further treatment, apparently convinced that they are going to improve with another series, I wonder whether such an attempt might be tried, with some benefit, in a situation which, for them, is full of suggestions as to what may happen.

DR. JOSEF A. KINDWALL, Wauwatosa, Wis.: I have not tried the use of hypnosis. The results might be illuminating, since there is a large element of suggestion in the treatment.

DR. DAVID SLIGHT, Chicago: I should like to ask how many patients had simple vomiting, as such, and how many had nausea without the vomiting. I may

have missed the description of the actual conditioning process, but I should like the authors to inform us as to what aspect of the alcohol the patients were averse. Did they become averse to the smell of the liquor, to the sight of it or to the mention of the word?

DR. JOSEF A. KINDWALL, Wauwatosa, Wis.: I shall answer the last question first. The conditioning was to the sight, smell and taste of alcohol. Patients also displayed an aversion to the clinking of glasses, the popping of corks. They would pour out smaller and smaller amounts of liquor as time went on. Sometimes they would pour out a drink, say "Here's to you," and end by drinking only a little. I think it is better to give the alcohol very slowly at first and let the patient smell it, put a little in his mouth and swish it around. It is the taste that counts, really. Later, when he begins to establish an aversion and is given a rather large drink, I suppose there is some gastric irritation connected with it. But, the man whose case I described, the man who had electric shock treatments after the conditioning therapy, had a high degree of aversion to the alcohol. He would claw at his mouth as though it were on fire. I had another man who could not swallow the alcohol or get it down. The aversion is a very real thing when it is present. The first man was given a small drink, from which he vomited five minutes before I gave him the injection. I delayed the injection and let him smell and taste the alcohol. It is not often that one gets such a strong aversion. Some people do not acquire it, and the treatment should be evaluated in these terms. The patients have real nausea, not only vomiting but shuddering and all that goes with it.

With regard to giving alcohol intravenously, such a method would by-pass the mechanism which is invoked in establishing the reflex. To introduce the drug directly into the blood stream would immediately affect the nervous system. There would be no chance for the conditioning mechanism (that is, rejection by the stomach) to take effect. I suppose one would have there the same situation as in the case of the woman I mentioned, who held her nose until she got the drink down. That would be a sure way of getting drunk for a person who had an oral aversion.

There is no doubt in my mind that the patient's fundamental sincerity and willingness to fulfil the conditions of the treatment is of tremendous importance but that one great advantage of this form of treatment is the distaste for alcohol which it arouses in the patient. In other words, I do not believe the value lies in conditioning alone. Even a mild aversion is of value, because the patient has something there that he has worked hard for, has suffered for and has invested his money in. I don't know exactly how to explain this in terms of reflexes, but certainly it means something. If a man puts himself wholeheartedly into something of this sort, it may arouse his stubbornness in favor of abstinence, because he has worked so hard for it, and he may struggle hard to maintain it. The element of sacrifice is there, too, as I mentioned in the paper. The patient pays a pretty stiff price in discomfort, and I think it relieves him of his feeling of sin; perhaps that makes it easier for him. I am also convinced that psychotherapy is important. The conditioned reflex treatment is only a means to an end, that is, to make it easier for the patient to leave alcohol alone. But the case of the woman I described illustrates that no matter how strong an aversion there is, if one needs alcohol enough one is going to take it. Since we did not solve her fundamental problem, I think we were fundamentally in the dark all the time. She is an extremely inadequate person, and though she is now devoting herself a great deal to Alcoholics Anonymous, she is often terribly "fed up" and unhappy. She is a lazy person and says so herself. She is in great danger all the time; but, after all, we have given her home a little respite, and the children ought to benefit to some extent from that.

The case of the second man I described is relatively simple. He is a stolid, simple person, who did not reveal any conflicts that we could get at. He is married, has a very nice wife and a child. He is well situated financially, has his cronies, likes to hunt and fish, but he drank just the same. Well, he acquired a strong aversion, has not gone back to drinking, is delighted and is rather simple and naive about it. That he has established an aversion to alcohol is the important factor. He was given little psychotherapy in the ordinary sense. We did not go into his problems at all, nor did he reveal any. There are a great variety of cases. In extreme cases the patients have deep-seated conflicts. Psychotherapy, reeducation and solving of the fundamental problem would perhaps result in greater response. But the relief that these persons feel when an aversion is established is amazing.

The Multiple Choice Rorschach Test as a Differential Diagnostic Tool. DR. PHYLLIS WITTMAN, Chicago.

The present study is an analysis of data obtained from use of the multiple choice form of the Rorschach test (as an individual rather than as a group technic) in the differentiation and diagnosis of psychiatric types. The data on 3,150 psychiatric patients, 883 attendants, 172 professional adults and 100 teen-aged Girl Scouts were analyzed for this study.

Test averages for the various groups ranged along a continuum, with the rating for the patients with hebephrenic schizophrenia at the lowest extreme and those for the professional adults at the other. The results for the subjects of the other schizophrenic subtypes (exclusive of the paranoid) ranked at the bottom, near those for the hebephrenic patients; then came the averages for the patients with constitutional and affective behavior reactions, followed by those for patients with organic lesions and for the nonpsychotic, paranoid and extramural subjects, in that order.

The most significant observation is the position of one of the psychotic groups (paranoid), which ranked in one of the top positions, above the group of patients who were classified as nonpsychotic. This position of the paranoid psychoses, including the condition diagnosed as paranoid schizophrenia, as well as the paranoid states, is in striking contrast to the poor level of the other schizophrenic subtypes.

Observations on the present levels of adjustment of both intramural and extramural subjects and study of the social service histories of the intramural groups suggest that the type of inner adjustment evaluated by the Harrower-Erickson Rorschach test is something that might be labeled "personality integration." (Personality integration, as the term is used here, implies an intrapersonal harmony of the components making up the personality as it effects the inner adjustments of the person.)

This paper presented the use of a psychologic technic as a differential diagnostic tool and concluded with an explanation of the value of diagnosis and the need for accurate and clearcut classificatory concepts from the research worker's point of view.

DISCUSSION

DR. A. A. LIEBERMAN, Elgin, Ill.: The clinical psychiatrist of the present day has come to rely tremendously on the exploring advantages of the original full Rorschach test. Especially is this so in undertaking any intensive analysis of the personality bordering on the psychotic state. The orthodox psychoanalyst, for example, has come to order a full Rorschach test in a case of incipient schizophrenia, as an internist might request a blood count. Yet a test which can be given and evaluated in five to ten minutes is of greater advantage to the psychiatrist responsible for the diagnostic study of large groups of patients, such as obtain in state hospitals, with often overwhelming daily admissions of new patients. The full Rorschach test, indicating in detail the analysis of a personality, is an extremely delicate instrument which can be administered only by a few highly trained persons. It follows, therefore, that any effective modification of the test must be one not only adaptable to mass use but possessing scientific validity as a useful diagnostic adjunct. The diagnostic utility of ratings must be dependent on the use of such ratings and signs as contributors to a clinical diagnosis, and not as a means of diagnosis themselves.

The modern clinical classification of mental disorders has, unfortunately, been oriented on the descriptive level of the "label," comparisons made on the basis of similarities, with differences often overlooked or studiously avoided. In this respect, the author is to be congratulated on having so succinctly delineated differences in mental reactions. Her paper is based on the tests of 4,300 persons, the great majority of whom were intramural patients who could be quickly tested the very afternoon of their admission. At the diagnostic staff meetings at Elgin State Hospital, this test has been of inestimable value, complementing to a significant degree whatever insight the clinician may have into the inner emotional life and constellation of the personality. Conspicuous in Dr. Wittman's presentation is the manner in which the schizophrenic patients stand off in statistically significant isolation; even more dramatic is the manner in which her modification differentiates the "true," or kraepelinian, dementia precox from the schizophreniform reaction types. The clinician has been only too well aware of these circumstances but has often adopted the path of least diagnostic resistance. The intensive research carried out by the author points to the need of a diagnostic inventory—undoubtedly many acute schizophrenic episodes might properly be included with the toxic-delirious excitements or recurrent affective states. In many cases paranoid schizophrenia may belong to the category of the paranoid state, which might also include paranoid projections not necessarily organized into a system of delusional ideas —they may be bizarre and unnatural, and yet the illness may not preclude a relatively normal adaptation to tests of reality.

At the Elgin State Hospital, this test procedure has found its place alongside the initial physical or mental examination.

DR. CHARLES F. READ, Elgin, Ill.: In the group of patients with hebephrenic and simple dementia precox, did Dr. Wittman find that there is any consistency in the grouping of the poor responses, or do they show merely a hit or miss selection, the patients perhaps exhibiting a lack of interest, attention, concentration, or whatever one pleases to call it?

DR. C. A. NEYMANN, Chicago: Dr. Wittman's paper gives rise to a great deal of speculation in regard to the Rorschach test. This test produces personal reactions from the patient, and its interpretation may also be subjective, though its advocates claim the opposite. In view of this, I congratulate Dr. Wittman on her paper, which allows a more objective interpretation. A question as to two points would seem to be proper. Can Dr. Wittman give us some information about the validity and the reliability of this new test?

DR. PHYLLIS WITTMAN, Chicago: There may be differences between these two types of schizophrenia and all other forms. One of the things my associates and I plan to do is to construct differential profiles showing on what particular cards and in what way the subjects with "process," or "true," schizophrenia differ from the subjects with schizophreniform and with other types of psychotic behavior reactions. The differential profile will indicate the characteristic response to each card for each group of subjects. We think we shall be able to find profiles that may distinguish hebephrenic and simple schizophrenia from the other types. Therefore I think that I can say "yes" to the question whether there were certain categories of responses which differentiated the process schizophrenia from the other types.

In answer to Dr. Neymann's questions: The validity of the scale is questionable. That is, the test is still a research tool. I myself give a different interpretation to the meaning of the results than that of Dr. Harrower-Erickson, which is an evaluation of emotional adjustment, since this does not fit the results which we obtained. The quality of personality integration is a better indication of what the test shows according to our results.

The reliability of the test is much less open to question than its validity. We have used the test on the same patient both before and after therapy and at other times as well. We have also used other cards, including Behn's and Harrower-Erickson's cards, as well as the original tests, and our results with the multiple choice scale are very similar to those with these forms of the test.

In answer to Dr. Slight's question: First, I did not emphasize that the modified multiple choice Rorschach test in no way takes the place, or can be considered the equal, of the original Rorschach scale. It is simply another tool, one that is more objective than the latter, and can be used by one less skilled in the Rorschach technic, or even by one not skilled at all. It can be given to a large number of patients in a relatively short period. Many patients who are uninterested and have to be urged to cooperate in many of our psychologic tests will respond rather well to the Harrower-Erickson Rorschach test. The purpose for which this particular scale was developed was to secure a test that was not so time consuming and not so difficult to evaluate as the Rorschach test, one which could be used as a weeding-out device for selectees and which could be given in a relatively short time and to a large group of persons. It was primarily developed for differentiating draftees who are too disturbed psychologically to be fit subjects for military training. We have adapted it to use with state hospital patients by using it as an individual rather than as a group technic. If one is familiar with the Rorschach test, one will notice that each choice is associated with a certain type of response which gets a similar weight on all the Rorschach cards —for example, an organized whole response, a purely color response or a definite form response.

The results for the psychopathic personalities disturbed me. I have been able to explain to my own satisfaction the other results we obtained. I do not have any explanation for those for the psychopathic personality. We found a number of such patients

who did very poorly. Then there were a number, although not quite so many, who did relatively well. I don't know why that should be. I wonder, however, whether it might not be related to the indefiniteness and looseness of the diagnostic concept "psychopathic personality." The term seems to be a catch-all for those states which do not seem to fit into any other classification.

Education, Reeducation and Psychotherapy. Dr. Jacob W. Klapman, Chicago.

Mental disorders may arise from repressions and distortions in the more somatically linked affect. There is also reason to believe that the affect and drive may show some constitutional weakness, giving rise in their extreme forms to what is often alluded to as "process schizophrenia." But, ordinarily, the breakdown in personality under apparently mild stress is importantly contributed to by the faulty conditioning of the apperceptive apparatus. This, of course, means faulty education.

As a result of acquisition and perception of facts, characteristic patterns of adjustment in the form of attitudes are brought into being. It is the attitude which carries the affective charge. It is, in fact, the bridge between the intellectual and the affective-instinctual life of the organism. Since attitudes are founded on experience, facts and supposed facts, the importance of the latter becomes apparent.

The perception and well balanced apperception and interpretation of facts in one's complicated environment, so that realistic and adaptative attitudes and adjustments can be made, are by no means a foregone conclusion and indicate the future tasks and present defects in the present educational institutions. The result is that, whereas individuation proceeds, there is not a corresponding growth of the self. The result might be described as "tubular intellect."

For the correction of these elements of maladjustment the reformation of basic attitudes is necessary. Unquestionably, there are mental disorders arising principally from distortions in the more somatically linked affect and instinctual drive. But even these are maintained through the sensorium and intellect, whose apperception of reality, originally thus conditioned, constantly maintains the affective disorder. In consequence, the person further exerts a selective action on his perceptions of reality, producing a fixed system of interaction.

In psychotherapy it becomes necessary to attempt to break this vicious circle. The analyst and psychotherapeutist allow, by their permissive attitude, the liberation or partial liberation of distorted affects. Through the transference and suggestions of the therapeutist, it follows that the therapy is accompanied with some enlargement of consciousness and intellect. There is still the possibility, nevertheless, that much of the drive thus liberated, much of the affective valence thus rendered available, may be incorrectly combined. This is the meaning of the transference neurosis. Chances for combinations which are socially well adapted and personally gratifying, too, are increased by placing at the patient's disposal a greater range of facts, attitudes and concepts. Furthermore, if the properties of these facts and attitudes are shown in their context and their relationships to the whole welter are carefully delineated, the choice is greater and more accurate. Obviously, this was the original intention of education and must again be made the aim of reeducation.

In individual psychotherapy, what reeducation takes place occurs largely through the transference. The patient accepts this orientation mostly on faith, because the therapeutist says so. He is, therefore, dependent on his therapeutist, and it may still be questioned whether analysis of the transference neurosis may not still leave much affective valence unsatisfied. Indeed, one often sees clinically schizophrenic patients who have recovered from the psychotic episode exhibiting no psychotic manifestations except what may be called "free floating anxiety."

It would seem, therefore, that the sensory-apperceptive-intellectual part of the personality must be equally reordered for optimum psychotherapeutic results.

DISCUSSION

Dr. Max Gitelson, Chicago: This discussion is somewhat handicapped by the fact that I have not read the paper, which is greatly condensed and presents a rich material. However, I think there is a considerable amount of validity in Dr. Klapman's description of the problems involved in psychotherapy. I obtained the impression, in listening to the paper, that the task of the psychotherapeutist is to help the patient in testing reality, that is, to help the patient reenforce and "revisualize," if I may use the term, the emotions involved in his illness in juxtaposition to the symbols and meanings related to these emotions. This, of necessity, in certain types of psychotherapy, perhaps most characteristically in analytic types, means the use of the intellectual powers of the patient. However, one cannot depend exclusively and finally on the intellectual powers. There is one absolute exception which will demonstrate my thesis that one is not utterly dependent on the powers of the intellect in treatment. The evidence lies in the fact that with children, especially extremely young children, in whom the intellectual capacity is formative, so to speak, it is still possible to do reconstructive psychotherapy with a minimum of dependence on symbols and with maximum reference to meaningful attitudes, postures and actions of the psychotherapeutist vis-à-vis the immediate postural responses, mimicry and general bodily activity of the child.

As a specific example, at present in the clinic at Michael Reese Hospital, my associates and I are treating a deaf mute, 4 years old, who is making remarkable therapeutic progress by means of communication which is symbolically understandable, though consisting only of postural attitudes and physical activity expressive of the child's interpersonal attitudes and capacity for relationship. The inability of the child to communicate and to symbolize by the usual verbal means has been no barrier to treatment.

Dr. C. A. Neymann, Chicago: It has been my experience in treating patients with neuroses that the most intellectual patients do not necessarily make the most rapid recovery. Frequently, the dull and backward make a quicker recovery. This certainly has been true of my latest experiences at the Veterans Rehabilitation Center. The woman who exhibitied a paranoid state in connection with her teeth, because she believed the dentist had used the wrong teeth in making a denture, certainly was stupid, if not feebleminded. Such patients generally are not classified as paranoid but, rather, as feebleminded with paranoid trends. Probably because of the highly selective symbolism and her lack of intellectuality, she made an unusually quick recovery. In other words, there was a decided interrelation between her stupidity and her acceptance of a simple factual explanation.

Dr. Jacob W. Klapman, Chicago: What the discussants have said is much to the point. There are undoubtedly many patients whose personality disorders can be adequately treated by the means mentioned, but

I am impressed by the fact that there are patients who have a very poor object relationship and are interested in nothing, and one scarcely has a handle to their personalities. They have not developed any real interest in the world. The emotional life has, therefore, found few points of attachment, with a tendency to curl up on itself in a condition of narcissism. I have speculated that the antidote may be an attempt to reeducate with a view to draw out the affect and anchor it securely to objects in the environment. That is the biologic significance of education, the task of reeducation and a prime consideration in psychotherapy.

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

BYRON STOOKEY, M.D., *President, New York Neurological Society, Presiding*

Joint Meeting, Jan. 9, 1945

Studies on Flying Personnel with Operational Fatigue: Studies on Dextrose Tolerance and Electroencephalographic Patterns. MAJOR BENJAMIN H. BALSER, Medical Corps, Army of the United States, and DR. BERNARD L. PACELLA.

One hundred members of the United States Army Air Corps with a disturbance diagnosed as operational fatigue were studied from the point of view of their electroencephalograms and dextrose tolerance curves. Thirty-eight per cent of these patients responded to the ingestion of dextrose with a "flat" curve in that the blood sugar did not rise significantly above the initial value and hypoglycemic levels developed rapidly. Eight of the patients whose oral dextrose tolerance curves were "flat" were studied by means of the intravenous administration of dextrose and exhibited sugar tolerance curves within normal range. Since the dextrose tolerance curves obtained with intravenous administration revealed no abnormalities, it is suggested that the "flat" curves after oral ingestion may not be indicative of a disturbance in the metabolism of carbohydrates but may be related to some disturbance in gastrointestinal activity whereby the absorption of dextrose is decreased.

Abnormal or borderline electroencephalographic records were obtained from 34 per cent of the patients, of which 20 per cent were abnormal in the resting state prior to hyperventilation. No significant correlation between the electroencephalographic abnormalities and the dextrose tolerance curves was apparent.

DISCUSSION

DR. RICHARD BRICKNER: I wish Dr. Pacella would say a word about a matter which frequently puzzles me in reports on men like these, who apparently have definite somatogenic disturbances, in this case fatigue, which would seem to be ample cause for the symptoms. Usually it is asserted that there is a psychogenic disturbance as well, but often the proof of this appears to be unsatisfactory. For example, some of the men in the South Pacific who had malaria, dysentery and extremely fatiguing experiences are spoken of as having psychogenic disturbances. Discussion on this point would be welcome.

DR. LAWRENCE S. KUBIE: I wonder whether it is wise to use the concept of "operational fatigue" at all in a scientific discussion of this problem. There can be no question that the term has considerable practical value in the military setting, for to label an illness as a neurosis has certain automatic results on such matters as a man's flying status, his earnings and his veteran's rights. It was to avoid this that the Army devised the term "operational fatigue." It might equally well be called anything else. Therefore when I heard Dr. Pacella say that this condition is due half to emotion and half to fatigue, I realized the danger of accepting this scientifically meaningless term as a conceptual basis for scientific investigation of the problem. This can lead only to confusion.

DR. MARGARET A. KENNARD: I should like to ask Dr. Pacella whether he has made quantitative determinations of the percentage of alpha activity. The reason I ask is that my colleagues and I have made determinations on patients with delirium tremens who show many such symptoms—sleeplessness, anorexia, extreme "jitteriness" and hyperactive knee jerks, and these patients have a high percentage of fast activity and far less alpha activity than do normal subjects. We also have some indication that patients with other disturbances associated with intense anxiety who show such symptoms as tremor and increased reflexes have an increase in fast, 20 to 30 per second, activity.

I should also like to ask whether the electroencephalograms were obtained before, during and after intravenous administration of dextrose. If I remember rightly, in Feinsinger's work on the electroencephalograms of a normal group, there was a much higher percentage of abnormality in the electroencephalogram of the subject when the glucose levels were low than after the intravenous administration of dextrose.

DR. HAROLD G. WOLFF: Will Dr. Pacella discuss for us the implications of his work?

DR. BERNARD L. PACELLA: The question which Dr. Brickner and Dr. Kubie raised with regard to the scientific validity of delimiting a clinical syndrome designated as operational fatigue is an important one. I do not consider myself fully qualified to judge the validity of such a classification because of my limited clinical contact with the personnel of the Air Forces. I might, however, refer to the observations of medical officers in the Army Air Forces that this syndrome, which they describe as "operational fatigue," appears in a man who has been flying at least several hundred hours and after he has been on a number of combat missions. Hastings differentiates between the men who "break" early and the men who "break" late. He states that the former generally exhibit anxiety features before they have been involved in much combat activity, and he finds that they usually have shown neurotic traits earlier in life. This group is usually unfit for further combat flying. However, the men who break late, after they have been through a number of harrowing and fatiguing experiences, are classified as having operational fatigue. They always seem to have a depression, in some cases rather severe. They practically always have a gastrointestinal disturbance, in addition to the symptoms I have already mentioned. The diagnosis of operational fatigue is not made unless, so far as can be determined, these men have shown fairly stable personalities all through life, in contrast to the men who break early, in whom instabilities of personality have prevailed previously.

I am grateful to Dr. Kennard for the questions which she has raised. First, the question whether dextrose was administered before the electroencephalographic recording: It was impossible for us to carry out this

procedure because of the necessity of making electroencephalographic studies on large groups of patients in very short periods. We realize that there may be a source of error here, but it is doubtful whether it would significantly alter our results.

As to the question about the percentage of alpha activity in our records: We did not carry out quantitative studies on this point. With respect to the effects of anxiety or tension on the alpha waves, I think there may be differences in the effect between severe anxiety, as observed in the neurotic patient, and ordinary tension as it appears in normal persons or in other subjects who come into the electroencephalograph room for the first time. In the last-mentioned subjects one usually sees a diminution in the alpha activity, whereas in patients suffering from severe anxiety we have often observed a high amplitude, high incidence alpha rhythm. This, in fact, was illustrated in case 2, in which I pointed out the high frequency of alpha activity over the occiput.

Dr. Wolff inquired about the implications of our results. We are presenting them merely as observations at present, and we are hesitant to proceed further with theoretic considerations as to the meaning of these observations. The report is a preliminary one, and we have avoided much discussion of the possible implications. One or two points were brought out: First, there is a possibility that in some of these cases the disturbance might be related to a concussion state. However, this is largely conjectural. Some of the electroencephalographic records have resembled strikingly the patterns observed with concussion syndromes, but there, again, such tracings are essentially nonspecific and cannot be offered as valid evidence of such a condition. If we were able to study these patients over a longer period, we should have more evidence along these lines.

Second, studies of the blood sugar suggest that the explanation may be a low rate of absorption of sugar from the gastrointestinal tract, although other factors may play a role in the production of the "flat" oral sugar curves.

Camptocormia: A Functional Condition of the Back in Neurotic Soldiers. LIEUT. COL. S. A. SANDLER, Medical Corps, Army of the United States.

Camptocormia is a hysterical phenomenon seen during wartime in certain neurotically ill soldiers.

1. It is manifested by pain in the lumbar area and by a bent trunk. The condition may or may not be precipitated by trauma and is of functional origin.

2. In cases of this syndrome there is not only adoration of but a suppressed ambivalent irritability and hostility toward the father. There is a strong overidentification with the father, who also generally had symptoms referable to the back. In the only 3 cases in our series in which the mother had serious trouble with her back it is remarkable that the fathers were either killed or died before the patient was 5 years of age; therefore the mother not only fulfilled her own part but assumed the masculine role of the absent father. This gives rise to speculation regarding the effect of the death or absence of the father on the psychosexual development of these men.

3. The onset of this back-bending phenomenon is concomitant with or preceded by impotentia, which I believe is rather general in camptocormia and is probably indicative of the soldier's latent homosexuality and castration anxiety.

4. The ambivalent feeling toward the father reflects itself toward authority in the military situation, with resulting projection of resentment on commissioned and noncommissioned officers. The military situation is the source of constant threat and danger to the ego, which continually strives for its safety and protection. When the pressure becomes too great, the ego wilts, and symptoms of camptocormia develop. We have observed that when these soldiers find asylum from the rigors and dangers of war by admission to an Army hospital, with knowledge of subsequent discharge from the service, this is sufficient to produce disappearance of symptoms.

5. This condition of camptocormia not only is a phenomenon in military life but is occasionally seen in civilian life after industrial and other types of accidents, but it is frequently unrecognized.

This paper was published in full in the July 1944 issue of *War Medicine*, page 36.

DISCUSSION

DR. E. D. FRIEDMAN: It is interesting to hear Colonel Sandler speak of this condition, for during World War I there were a number of cases. I saw some of them; I also have seen some cases in which the disturbance resulted from an industrial accident. As is generally known, the term camptocormia was coined by Babinski after the last war; he was fond of Greek derivations. In the same volume in which he described camptocormia, he described pithiatism—his term for suggestion neurosis. He also is responsible for the term adiadokokinesis.

Bent back is a nonorganic syndrome which is stubborn to therapy and persists for a long period.

I should like, without disparaging the dynamics suggested by Colonel Sandler, to bring into relationship with this syndrome the case of a child with encephalitis whom I observed at Bellevue Hospital (perhaps Dr. Denker remembers the boy). As a result of this illness not only did typical paralysis agitans develop, but he began to stoop forward more and more, so that he became almost a quadruped. Thinking in terms of primitive patterns of activity, one would say he had made a phylogenetic recession to the quadruped phase of locomotion. One sees other release phenomena in the wake of encephalitis—for example, the rhythmic protrusion of the tongue, as exemplified by the panting dog, and periodic fishlike opening of the mouth. It may be fair, therefore, to state, in the sense of Wilson, that these patients with bent back make a similar phylogenetic recession to the level of the basal ganglia. It would be interesting to follow these patients for a time and see whether one can demonstrate such a mechanism.

DR. ISRAEL STRAUSS: I am much interested in Colonel Sandler's paper. It is difficult to explain attitudes such as this on a functional basis. Colonel Sandler's expression of the dynamics is satisfying. It is satisfactory to persons who are familiar with the freudian concept. By those who are not, who do not understand them or who insist that one must look for something else these patients will often be regarded as malingerers. Personally, I hesitate to make a diagnosis of malingering in civilian life. I have not dealt with the soldier, but I have always felt that most malingerers have a psychopathic personality, even though it appears to the casual observer that the malingering is motivated by self interest. I mention this because Colonel Sandler says these patients became erect the minute discharge was in view. As Dr. Friedman said, it would be interesting to follow these men. The difficulty with much of the work presented at present by Army officers is that there is little follow-up observation. What I say with regard to Colonel Sandler's paper applies also to the previous paper. It is the follow-up study which will

tell whether the ideas expressed in the paper have validity and will offer the explanation. However, there is one thing one must be careful about. In the first case presented by Colonel Sandler there was a history which would generally be interpreted as indicating a protruded intervertebral disk, the result of repeated trauma to the back caused by the lifting of excessive weights. As a matter of fact, only recently a United States soldier who was discharged was brought to me because he had recurrent backache. He had been hospitalized frequently, and he was bent down and could not stand up. When he received his discharge, he stood up. However, I felt there was something more than a psychologic situation, and he was sent to one of the local hospitals, where the intern told his chief there were no physical indications in the case, that the man's trouble was in his head, not in his back. The soldier was discharged. I met the attending physician, who is an excellent surgeon, and I said, "Too bad you were listening to the resident; suppose you go in with the knife and see whether it is in the head or in the back." He found a large intervertebral disk protruding, and the man is now cured of the camptocormia. This is not told in a derogatory way; it is said to illustrate the need of being on guard, and no one knows that better than my friend Colonel Sandler. I mention this only in regard to the first case; in the others the history did not lead one to suspect a protruding intervertebral disk.

DR. BYRON STOOKEY: I think that is why Colonel Sandler put the case on record; I believe it is the only one in which the patient escaped the Army without being operated on!

DR. IRVING J. SANDS: I should like to ask Colonel Sandler whether any psychometric tests were made on these patients; and, if there were, what were the intellectual levels?

My experience in World War I leads me to believe that this condition is rare; among some 3,000 patients in ward 55 of General Hospital No. 1, and among the many patients that I have seen at the outpatient department of United States Veterans Hospital No. 81 over a period of eight years, I do not recall a single case of the disorder. I am, however, much interested in the intellectual level of Dr. Sandler's patients, as I believe it will bear a definite relation to the manifestations of this conversion hysteria.

DR. RENÉ A. SPITZ: In these cases there are two satisfactions which the patient gets, or, rather, two aims which he is able to achieve with the help of his bent back. 1. In military service these men, who are extremely ambivalent and unctuous when examined by their officers, achieve through their bodily position the possibility of avoiding standing at attention; in other terms, their bodily position is disrespectful to their officers because they do not stand at attention, but at the same time they bow respectfully. 2. In civilian life these men, who seem to show a previous history of sickness, are mostly impotent. This bodily position makes intercourse impossible and serves to justify their avoidance of it.

DR. EDWIN G. ZABRISKIE: I came in at the end of Colonel Sandler's paper; so I shall speak on only two points: One is that I never saw a case of camptocormia in France or in this country, my experience being the same as Dr. Sand's in this respect. I have heard of the condition, but it was never my fortune to run into a case. Second, in the Army, we recognized only two types of malingering in France; one was the self infliction of a wound, and the other was straggling on the way to the front. The French recognized this and dealt with it strictly, by shooting the men; as a result, the practice ceased to be a problem. In the United States Army they did not go quite that far.

DR. BYRON STOOKEY: May I ask Dr. Strauss and Dr. Friedman, who have had a vast experience, how many cases they have encountered in their civilian practice. I ask because I have not encountered any, nor do I remember having seen any in my service in the last war in the British army, in 1915 and 1916, or in the United States Army, in 1917, 1918 and 1919. I should like to know whether Dr. Strauss and Dr. Friedman have encountered any cases in civilian practice.

DR. ISRAEL STRAUSS: I have not.

DR. E. B. FRIEDMAN: I have seen 2 cases, and I think Dr. Brock has seen 1 case, as a result of industrial accidents.

DR. BYRON STOOKEY: The practices of Dr. Strauss and Dr. Friedman represent an enormous clinical experience; so it must be a rare condition.

DR. LAWRENCE S. KUBIE: Any dramatic symptomatic disturbance such as this exerts a strong suggestive influence on other men, particularly when men are kept together over a long period or the men are of low mentality and show considerable passive suggestibility. This bears out the dynamics which Colonel Sandler has described. I should not be at all surprised if such cases occur in sudden outbreaks in groups of men, among whom group contagion is active. In certain of the cases described by Colonel Sandler, the role of group suggestion was particularly clear, as in that of the man who came in with headaches but who ended with severe camptocormia.

I should like to make one other point; a chronic organic lesion of the lower part of the back, such as a protruded disk, will gradually become interwoven with all the emotional disurbances latent in the personality. In such a situation it is difficult to know which attacks are hysterical and which are organic. That camptocormia should develop subsequent to a long history of pain in the lower part of the back is wholly understandable.

DR. RENATO ALMANSI: I had the opportunity of observing a case of camptocormia in a Negro soldier several years ago. He was a man of low intelligence and was very ignorant, and there was a definite reason in his surroundings for the development of his symptoms, inasmuch as he was dissatisfied with his superiors and officers. In that particular case I was stern with the patient, not because I assumed he was a malingerer (I was perfectly satisfied that he was not), but because I thought that his condition would be benefited by a firm attitude. Thus, by taking away from him all the satisfactions that his condition had given, I was able to correct his camptocormia in a few days.

Colonel Sandler mentioned that the condition of his patients cleared up as soon as they were discharged from the hospital. I wonder whether a firm attitude toward them would not have achieved the same result.

DR. BYRON STOOKEY: May I ask Colonel Sandler how frequently this condition is encountered in Army camps of comparable size and whether he is aware of any Army statistics which would be of interest. I heard him refer to 2 other cases, the assumption being that, so far as he knows, no other cases have been reported.

DR. ISRAEL STRAUSS: I should like Colonel Sandler to state how many men with this disorder were in camp at one time and what their contact was with each other. I ask that in connection with Dr. Kubie's question.

LIEUT. COL. S. A. SANDLER: I wish to thank the discussers for being so charitable and for not trauma-

tizing me too much. I shouldn't want to go back to camp with camptocormia!

Dr. Strauss's contention that it is possible for these patients to have a lesion of the cord is quite correct, except in the case of the soldier he discussed—that man had no radicular signs or any localized pain. Also, it is to be noted that he had four attacks in civilian life, previous to induction into the Army and he specifically pointed out that at the onset of three attacks he was with some one to whom he had a strong emotional attachment, once his father, once his wife and the third time his best friend.

Dr. Strauss's contention that suggestion has considerable influence in this condition is correct; because of its hysterical character, suggestibility, as far as other soldiers are concerned, was indeed a difficult problem.

I watched these patients for a considerable period. I was "between the Devil and the deep sea." As a staff officer (I happen to be not only a medical officer but a staff officer) part of my duty is maintaining and enhancing the morale of the training center, and therefore on many problems I see eye to eye with the line officers. We wanted no man discharged from the service unless he was really ill; on the other hand, there was the problem of how to control the possibility of mass suggestion. It is true that when these men started coming in, most of them seemed to be from the same companies, and there is no question but that there was an element of suggestion.

In reply to Dr. Stookey, may I say there has been little published on this condition? The largest series consisted of but 2 cases, reported by Lieut. Col. Percy G. Hamlin (Camptocormia, The Hysterical Soldier's Bent Back, *Mil. Surgeon* **92**:295-300 [March] 1943). However, when, at a conference of neuropsychiatrists in a certain camp a few hours ago, I said I was coming here to present these cases of camptocormia, they all agreed that they had seen a number of such cases. One medical officer facetiously remarked: "If you need cases to present, I can let you have about 30 from my ward." Although I have presented 19 cases, I have seen almost twice that number.

I learned something here tonight from Dr. Friedman (as I usually do). Only today one of the medical officers in another camp, referring to camptocormia, stated: "While your men with camptocormia are all bent forward, I have a man in the opisthotonos position. How do you account for that?" I replied that in the camp with which I was associated they all seemed to follow the same pattern; however, I think Dr. Friedman's suggestion that the condition is an encephalitic manifestation might be correct.

Dr. Sand's question is a good one. He is correct in his assumption that these men had low intelligence quotients. Their average period of schooling is about seven years in grade school, as compared with a group of somnambulists which I reported on at the meeting of the American Psychiatric Association last spring, whose average educational level was about three years of high school. The proportion of Negro soldiers was much greater than that of white soldiers (I think my reply to Dr. Sands also answers Dr. Kubie).

One of the discussers asks whether firmness would have been helpful. The answer is: "No!" Neither firmness nor kindness seems to have any effect so far as cure is concerned. There is a kind and understanding psychiatric chief in the station hospital, and I must reiterate that no amount of kindness seemed to obtain results, unless that kindness was associated with a discharge from the service! Treating these soldiers with firmness and pointing out to them that they were expected to remain in the Army only seemed to complicate matters; but, as previously noted, kindness or firmness, if associated with a certificate of disability discharge, appeared to be the answer.

Distant Secondary Circulatory and Vasomotor Reactions to Accidental Electric Shock. DR. GEORGE H. HYSLOP.

Alexander (*M. Clin. North America* **22**:663, 1938) stated that 25 milliamperes or more may produce permanent damage to nerve tissues and blood vessels.

One may define direct primary effects as limited to tissues traversed by the current. Indirect, or secondary, effects are those which occur in other tissues as a result of a reaction originating in tissues traversed and directly affected by the current.

Weeks and Alexander (*J. Indust. Hyg. & Toxicol.* **21**:517, 1939) demonstrated that the current chooses the shortest path from contact to contact without deflection by anatomic landmarks (thus indicating that the body acts as a "structureless gel"). They also demonstrated that in tissues adjacent to, but at a distance from, the current main path the effective current conducted rapidly decreases; that is, there is practically no diffusion of the current at a distance from its main path. As for blood vessels, it has been shown by Echlin (ARCH. NEUROL. & PSYCHIAT. **47**:77 [Jan.] 1942) that when the current traverses arteries there is an initial constriction followed by a period of dilatation, which may be extreme and prolonged and cause secondary hemolysis of the blood in the veins. These reactions are limited to vessels traversed by the current.

Alexander (ARCH. NEUROL. & PSYCHIAT. **47**:179 [Jan.] 1942) stated: "In hand to hand contacts cerebral changes are not due directly to the current but are caused by the prolonged circulatory disturbances produced by passage of the current through the heart and the endings of the vagus nerve."

Instances are known in which no loss of consciousness occurred and the current pathway did not reach the brain, but within a few minutes to two or three days the victim manifested signs of focal reaction in the brain. As yet no satisfactory explanation has been offered for such delayed and distant tissue reactions.

Scheinker (ARCH. NEUROL. & PSYCHIAT. **52**:43 [July] 1944) presents certain conclusions which are perhaps germane. Scheinker's paper is concerned chiefly with the effect of mechanical trauma on blood vessels. However, he points out that profound circulatory disturbances may be seen in regions remote from the direct influence of the irritant stimulus, thus indicating that the stimulus is probably transmitted over a neurovascular network to the distant subdivision of the vascular tree. If there is circulatory stasis, there is local accumulation of carbon dioxide, which is a particularly active vasodilator. If it continues to accumulate, there are further vascular dilatation and increased permeability of the vessel wall, with actual degeneration and necrosis of the vessel walls if the alterations are sufficiently severe. Thus, the essential vascular factor for involvement of surrounding tissues is the increased permeability of the vessel wall.

If current traverses the cervical sympathetic fibers, it is not unlikely that the vessels of the brain may be affected. When the splanchnic and abdominal sympathetic ganglia are violently stimulated, with possible spread of the impulses to the cervical sympathetic fibers, reaction of the cerebral vessels could occur. There

might be immediate transient symptoms of focal nature if the effects on the vessels of the brain were limited to brief spasm. If the vessel wall were to suffer structural damage, with impairment of permeability, effects on surrounding brain tissue might be delayed, so that focal clinical symptoms would not be evident for even a few days.

DISCUSSION

DR. WILLIAM A. GEOHEGAN (by invitation): Dr. Hyslop has presented an interesting possible explanation of some of the indirect and delayed reactions to electric shock. As he has pointed out, Weeks and Alexander showed that electrically the body behaves as a structureless gel and that therefore most of the current passes directly between the points of contact and the current passing outside this path is relatively small. It might be noted that the apparatus they used permitted measurements of current only as small as about one twentieth of the current at the point of maximum current density in shocks of lethal magnitude; in view of the fact that in certain circumstances extremely large shocks may be tolerated without causing ventricular fibrillation, it is quite possible that in some cases there may be cerebral damage due to the current itself. However, it is clear that in a considerable number of cases, as Dr. Hyslop has pointed out, there are cerebral effects that cannot be explained on the basis of the passage of the electric current itself. It has been generally considered, as he has pointed out, that these changes are related to circulatory factors, but no one has ever described the exact nature of these alterations except to note the results of stimulation of the vagus nerve. Because of the importance of the sympathetic chain in the control of cerebral vessels and its position in the path of greatest current density in arm to arm shocks, it is reasonable to assume that it might have considerable influence on the vessels in cases of electric shock. It is not necessary to assume any permanent tissue damage in the sympathetic chain. As Speidel has shown in moving pictures of living tissue, with even slight electric shocks it is possible to get retraction of nerve endings and subsequent growth, so that even a small shock may change the pattern of the sympathetic response. If one attempts to explain the effect on the brain entirely in terms of the effect on the sympathetic nervous system and, further, on the impulses in the cervical portion of the sympathetic chain, the exact pattern is hard to visualize. If one were to assume that the change is due to cessation or diminution of impulses in the cervical sympathetic chain, one would have to explain why the same condition does not arise in cases of bilateral stellectomy. If one were to assume that it is due to an increase in activity, one would have to explain why the same situation does not arise with irritative lesions of the cervical sympathetic trunk. Therefore it does seem hard to explain the picture on the basis of altered impulses in the cervical sympathetic chain itself. However, it is reasonable to assume that the altered function in the sympathetic trunk may be contributory in producing vascular changes, which, added to those in the systemic circulation, might cause such effects as those described. Animal experimentation to determine the exact nature of this altered function might be undertaken; some of the possibilities might be fairly easily investigated, while others might be difficult. For example, one might record electrically from the cervical sympathetic trunk, or one might study the vessels in the brain before and after shock, both with and without previous stellectomy. These experiments would give evidence of a positive nature in some cases and of a negative nature in others, because performing the stellectomy would merely remove the effect of the cervical sympathetic chain and one could not then study directly the effect of inhibition of the cervical sympathetic chain as compared with the effect of leaving it intact. This might be done in a sufficiently large series by comparing results with observations on normal animals. I believe that investigation of this problem by means of animal experimentation might lead to interesting observations on the action of the sympathetic nervous system in such cases as Dr. Hyslop has described.

DR. BERNARD L. PACELLA: I should be interested in knowing Dr. Hyslop's opinion regarding the possible distant effects of electric shock therapy on the central nervous system, inasmuch as controversial opinions are expressed in the literature. However, it may be noted that in patients who have been accidentally "shocked" the voltage required is usually greater, and the time of passage of the current through the body is generally longer, than in therapeutically "shocked" patients.

My associates and I have not observed in any case clinical evidence of focal cerebral lesions; yet the electrodes are always put directly on the head, so that the current flows through many of the important structures of the brain. We do find electroencephalographic evidence of some disturbance weeks after patients have received electric shock therapy, but we have not yet observed electroencephalographic evidence of focal damage.

DR. GEORGE H. HYSLOP: One does not like to lay an egg without sitting on it long enough for it to hatch. I realize perfectly well that this hypothesis has as yet no experimental demonstration. I laid this egg hoping that with the passage of time and the eventual availability of experimental animals and all the other requisites, physiologic corroboration or refutation of this hypothesis could be made. In addition to the particular line of animal experimentation mentioned by Dr. Geohegan, there would be another, namely, that the animals subject to the experimentation should have the current travel from hindlimb to hindlimb or directly through the trunk, and presumably directly affecting the thoracic and abdominal sympathetic ganglia. I presented the subject in the hope that it might intrigue at least those who have had to deal with the clinical effects of accidental electric injuries.

Apropos of Dr. Pacella's discussions, there is a fairly abundant literature on the histologic effects of electric shock on the brain. These effects are identical with, and less in degree than, those associated with metrazol shock, and most of the damage is not due to the burning effects of the electric current. There is abundant evidence, translated from the animal and corroborated by autopsy on persons who have died, sometimes of cardiac but not of cerebral cause, that electric shock produces diffuse damage which from a clinical standpoint may be only transient.

As to the final clinical reactions, some have been bandied about by word of mouth but are not in the literature. One hears of patients who, after a certain period, lose the higher intellectual abilities and are disqualified from certain types of occupation. It is a well recognized fact that some of the electroencephalographic effects may persist for months after electric shock treatment is over—evidence that this treatment is not to be taken lightly, any more than a demonstrable cerebral reaction to infection or injury can be passed over lightly.

CHICAGO NEUROLOGICAL SOCIETY

RALPH HAMILL, M.D., *President, in the Chair*

Regular Meeting, Jan. 9, 1945

Arnold-Chiari Deformity in an Adult Without Obvious Cause. DR. PAUL C. BUCY and DR. BEN W. LICHTENSTEIN.

The term "Arnold-Chiari deformity" is generally used to designate a specific modification in the configuration and location of the hindbrain. It is usually found in association with spina bifida or platybasia. Formerly looked on as a malformation, it is now generally conceded to be a deformity resulting from abnormal forces exerted within the craniospinal cavity. Its occurrence with spina bifida is believed to be due to abnormal fixation of the spinal cord, its roots and meninges. Its occurrence without obvious cause is unusual, and its early recognition is of practical importance, for great improvement in the neurologic picture follows surgical decompression of the craniospinal junction.

The authors report the case of an American Negro woman aged 40 who had had paresis of the lower extremities and the right upper extremity for approximately one and one-half years prior to surgical exploration. The weakness in the extremities was associated with sensory disturbances in her right hand and atrophy of the right side of her tongue. For many months she had been believed to be suffering from a vascular lesion in the medulla oblongata. Spinal puncture revealed complete spinal block. Suboccipital exploration revealed a typical Arnold-Chiari deformity, the medulla oblongata and the tonsils of the cerebellum being displaced into the upper cervical portion of the spinal canal. The right hypoglossal and spinal accessory nerves were found to be elongated and tense. After decompression the patient made an excellent recovery.

No evidence of spina bifida or platybasia was noted. Similar cases were reported by Adams, Schatzki and Scoville and by Aring. The clinical picture usually becomes fully developed about two years after the onset of symptoms. The symptoms fall into four groups: (1) those resulting from increased intracranial pressure, such as choked disks and headache; (2) those indicative of involvement of the lower cranial nerves; (3) pyramidal signs and sensory disturbances resulting from compression of the brain stem or the spinal cord, and (4) cerebellar signs.

DISCUSSION

DR. PETER BASSOE: In the 1 case without spina bifida in which autopsy was performed, I should like to ask whether the lower part of the spinal cord might have been fixed early in life by some other process, such as meningitis.

DR. GEORGE B. HASSIN: I should like to ask Dr. Bucy whether hydrocephalus does not usually occur with spina bifida as a manifestation of general hydrops of the brain, including the brain stem, and whether at the time of operation such signs were present. I should also like to ask Dr. Lichtenstein whether in cases of curvature of the spine, such as kyphosis or angular fractures, the spinal cord is stretched. Why are signs of hydrocephalus, which in cases of spina bifida are supposed to be due to pulling or stretching of the spinal cord, absent in the instances mentioned in which the spinal cord greatly deviates in following the spinal deformity?

DR. PAUL C. BUCY: Dr. Hassin is correct; the Arnold-Chiari deformity is commonly associated with hydrocephalus. It is, in fact, one of the common causes of hydrocephalus in children who have a meningomyelocele. In the present case no ventricular study was made prior to operation, and at the time of operation edema of the tissues was not observed. We therefore have no direct evidence as to the presence or absence of ventricular dilatation.

DR. BEN W. LICHTENSTEIN: In answer to Dr. Bassoe, I wish to state that many cases have been described in which the Arnold-Chiari deformity was found in adults at autopsy. This was generally in association with platybasia. In Aring's case no spina bifida was noted.

In answer to Dr. Hassin's question, the upward migration of the spinal cord is greatest in utero and in early infancy; therefore fixation of the spinal cord in an adult by a fracture of the spine or a callus does not lead to the formation of an Arnold-Chiari deformity.

Structural Changes in the Brain in Experimental Concussion. DR. W. F. WINDLE, DR. R. A. GROAT and DR. C. A. FOX.

Concussion is a transient state which sets in immediately on application of an adequate force to the brain. Its chief functional manifestations are unconsciousness and paralysis of certain neural components. Its histopathologic counterpart is a subtle intraneuronal disorganization. In cases of head injuries concussion is often combined with traumatic interstitial hemorrhage, contusion or laceration of the brain. We are not concerned with the latter types of injury, for we are dealing with simple, uncomplicated concussion produced experimentally in guinea pigs, cats and monkeys, usually under the influence of light anesthesia induced with chloralosane (preparation of chloral and dextrose). Our present report deals with changes in the central nervous system of these animals during concussion and with the cytopathologic sequelae after concussion.

We produced concussion by applying adequate force to the brain, either by means of a pendulum striking the head or through a hydraulic system connecting with the interior of the cranium. Our criteria of concussion were cessation of respiration and abolition of the corneal reflex. Electrical stimulation within the cat's brain by means of fine electrodes placed with the Horsley-Clarke instrument revealed the following facts: The excitability of nerve fibers was relatively unimpaired in concussion; the excitability of cranial motor nerve nuclei was impaired less frequently, to a smaller degree and for shorter intervals than that of supranuclear motor parts, such as the tegmentum of the brain stem, the hypothalamus and the motor cortex. Similar differential functional alterations have likewise been observed in rhesus monkeys subjected to concussion. Throughout our studies concussional changes in function set in at the moment the blow was delivered. Recovery of function occurred gradually.

Brains of guinea pigs and rhesus monkeys which were subjected to concussion were prepared for histologic examination. Staining was carefully controlled. In a few experiments the brain was fixed by perfusion with dilute solution of formaldehyde U. S. P. within a few seconds of the time the concussive blow was struck. Significant alterations in arrangement, shape and size of Nissl bodies of neurons were observed in these specimens. The Nissl bodies of some cells were fragmented and disarranged by the blow. In others they were clumped together as though agglutinated. Many neurons seemed to be unaffected.

In less than twenty-four hours after concussion chromatolysis of certain neurons began. Many cells showed marked changes in two days, reaching maximum intensity by the sixth to the eighth day. Progressive chromatolysis culminated in destruction of some neurons, but not all were affected to such an extreme degree. Not all neurons were affected equally by concussion. Primary afferent and primary efferent neurons of the cranial ganglia and cranial motor nerve nuclei were practically unaffected. It was easier to see changes in large than in small interneurons, although the latter were affected too. All concussive blows induced changes in the lateral vestibular nuclei and scattered large neurons of the tegmentum of the brain stem. With increasing intensity of concussion, the red nuclei, the nuclei of the trigeminal spinal tract and the medial vestibular and cochlear nuclei became involved. In the cerebrum, the large pyramidal cells underwent alteration in structure, but they did not show chromatolysis. The basal ganglia and the cerebellar cortex appeared to be unaffected. The amount of damage was proportional to the strength and the number of blows struck.

Concussive blows delivered at intervals of one week in guinea pigs produced as much as 50 per cent loss of neurons at such places as Deiters' nucleus and the red nucleus. No loss of cells occurred in primary motor nerve nuclei.

In most of our experiments, nerve fibers and myelin sheaths appeared to have received little damage. In the specimens which were struck the most severe blows, a variable amount of swelling was observed in the myelin sheaths, especially in the lower part of the medulla oblongata and the upper cervical portion of the spinal cord. With the Marchi degeneration technic, changes in myelin sheaths could be demonstrated after severe concussive blows.

Simple concussion produced no vascular changes. The water content of the brain was insignificantly increased. Effects of concussion were not those of asphyxia. A significant difference between the effect of concussion and that of cutting the axon was observed.

DISCUSSION

DR. R. A. GROAT: The only thing I might add is a statement about the relationship between anatomic and functional alterations. The distribution of concussional and postconcussional anatomic changes corresponded well with the distribution of concussional functional changes which we found in previous studies in cats. Whether or not the relationship between the anatomic and the functional changes which we have demonstrated is causal we cannot say. All we can say is that the cell changes indicate the ravages of a concussional force.

DR. GEORGE B. HASSIN: Changes of nerve cells following concussion have been observed in the human spinal cord, but not in the brain, where changes have been studied only experimentally. The authors' demonstration should be convincing that concussion may bring on almost total destruction of nerve cells in the brains of rabbits. In some of them, the changes were pronounced within six days after the lesion, while in the spinal cord of rabbits changes from concussion occurred sometimes within the first twenty-four hours (Ferraro, A.: Experimental Medullary Concussion of the Spinal Cord in Rabbits, ARCH. NEUROL. & PSYCHIAT. **18**:356 [Sept.] 1927). The authors demonstrated only parenchymatous changes and said nothing of the condition of the glia which produces edema in brains with traumatic lesions. Nor were the vascular changes, such as hemorrhages, emphasized. They were evidently absent. In any discussions of cerebral lesions—contusion or concussion—hemorrhage is always mentioned. Whether hemorrhages occur in cases of cerebral concussion in human beings is not possible to tell, as such cases have not been studied pathologically. It is admitted that concussion always accompanies contusion, but it is hard sometimes to tell which changes are due to the effects of concussion and which to those of contusion. In experimental work the task is easier, and one should be satisfied to know that concussion may cause disappearance of nerve cells.

DR. R. P. MACKAY: Were any histologic studies made on animals with subconcussive blows? Those of us who see patients with minor head injuries are often struck by the relatively serious functional (physiologic) changes which may result, such as severe headache, postural vertigo and "nervous" reactions. These symptoms are not psychogenic, even though actual concussion seemed not to have occurred, since the patient did not lose consciousness. It would be helpful in courts of law to know of any anatomic or pathologic changes to which such phenomena could be referred.

DR. A. EARL WALKER: I have followed this work with interest. It is a beautifully controlled study, one that has convinced us that cerebral concussion can be associated with histologic changes in the brain. I wonder whether these alterations may not be present in other parts of the brain. The cells shown had well formed Nissl bodies. In the smaller cells might there not be similar changes that could not be demonstrated by the present technics? There is also this point, that the nuclei involved are in that part of the brain where maximum stresses from a blow occur and where vascular effects are frequently found. All are acquainted with Duret's petechial hemorrhages, which occur in the floor of the fourth ventricle. I also wish to ask whether there were changes in the hypothalamus, since this region has been said to be involved in concussion.

DR. VICTOR E. GONDA: Did tremor occur in these animals, or did they survive long enough for it to be noticed? In boxers exposed to concussion somewhat similar to the type you describe there are many cases in which a typical Parkinson syndrome develops. Did these animals live long enough for this to be seen? Were the basal ganglia examined as to changes which might develop at a longer period after injury?

DR. W. F. WINDLE: I might say in answer to Dr. Hassin's question that the cases we discussed were those in which there were no hemorrhages, although in a few other specimens much stronger blows did produce hemorrhages. This picture of concussion is usually produced without any hemorrhage. Unlike our studies on the effects of asphyxia, in which marked glial proliferation occurred, we saw no such proliferation after concussion.

The question of edema, of course, comes up. We have recently run a series of experiments on the water content of the brain. It is interesting to note that we did find a little increase in the water content of the brain, but very little. In fact, after severe concussion in the guinea pig brain we found that it amounted to 0.5 per cent of the wet brain weight, of about 19 mg., or less than ½ drop.

Dr. Mackay asked about subconcussive blows. We did have animals which were given subconcussive blows. A single strong concussive blow led to extensive changes. A single light blow did not produce demonstrable changes, but when we superimposed other light blows

we obtained changes similar to those which followed a single concussive blow.

Dr. Walker asked about cells in other parts of the brain being affected. With careful search many small cells can be found showing similar changes. We simply demonstrated the larger cells because they are easier to photograph. We have not been satisfied that the histologic changes are the result of torsion and shearing of the brain in concussion. If such torsion does produce cellular damage, I should expect to see primary motor and sensory nerve cells involved, but this is not the case. Alterations after concussion were not periventricular.

We found evidence of functional alteration in the hypothalamus, but no structural changes have been demonstrated; perhaps we have not searched closely enough.

In reply to Dr. Gonda, we saw no tremors. The punch-drunk fighter we are not prepared to discuss at this time. We have some studies in progress on the cumulative effects of concussion. I cannot say anything about the basal ganglia in boxers.

Tridione: A New Experimental Drug for Treatment of Convulsive and Related Disorders. I. Pharmacologic Aspects. DR. R. K. RICHARDS.

In testing drugs for their possible value in human disease, the pharmacologist is almost always confronted with two principal handicaps: first, the innate differences of species in their reaction to drugs, and, second, the fact that in almost every instance the artificial condition created to test the drug differs from the pathologic condition which the drug is supposed to cure. Much of the pathology and nature of idiopathic epilepsy and related disorders is unknown, and investigators are still far from creating similar conditions in animals, although epileptoid seizures do occur spontaneously in some species. The testing for anticonvulsive properties is based on the production of convulsions by two principal means: drugs and electric shock.

The fact that a drug will suppress or prevent seizures induced by either of these methods in animals is not sufficient to indicate its usefulness in human therapeutics. Most depressant drugs in hypnotic doses are able to antagonize chemically induced convulsions or raise the threshold of the current necessary to produce a seizure. However, one must demand a greater specificity than is indicated by mere depression, inasmuch as such drugs frequently produce too great drowsiness in effective doses to be useful in therapeutics.

Tridione (3,5,5-trimethyloxazolidine-2,4-dione) was first studied as an analgesic and possesses considerable analgesic properties; these have been substantiated by animal experiments, as well as by clinical observations. In a study of a series of antispasmodic drugs which, in toxic doses, produced signs of marked central stimulation and convulsions in animals, it was noted that this compound, Tridione, was remarkably active in reducing convulsions due to the antispasmodics. This observation led to more intensive study of the anticonvulsant properties of Tridione. In its evaluation, both the drug and the shock method have been used to produce convulsions, although the chemical method seems preferable. The anticonvulsant should protect against convulsive, or even fatal, doses of a central stimulant in a dose which would not significantly impair the normal behavior of the test animals. Mice and cats have chiefly been used in this study, and metrazol has been found most useful as the convulsive agent.

The reaction of mice to metrazol and other convulsant drugs was shown by slides, together with the protective action of various dose levels of Tridione if given before the convulsant. If convulsions were produced first, an injection of Tridione almost instantly stopped them and saved the animal's life. An effective dose of Tridione would protect mice for about one hour against a certainly convulsive dose of metrazol. Phenobarbital, also known to be active against metrazol, was found to be somewhat more depressant than Tridione. Diphenylhydantoin has been reported to protect against metrazol convulsions only if administered for several days before the injection of the convulsant. The observations on cats substantiated those on mice.

In some studies convulsions were produced in rats by placing the electrodes on the head and using various voltages of the secondary coil of a Harvard inductorium to induce convulsions. The tests were rather crude, the thresholds referring to the prevention of full blown convulsions only. Tridione is effective in raising the threshold necessary to produce convulsions; this is also true of phenobarbital and diphenylhydantoin. In these studies, also, phenobarbital produced a greater depression than Tridione.

Even in view of the demonstrated activity of Tridione in experimentally induced convulsions, the proof of its therapeutic value must rest in the hands of the clinician.

II. Clinical Investigations. DR. M. A. PERLSTEIN.

This study represents a total of 47 patients who have been observed over a period of eight months, in the Children's Neurologic Clinic of Cook County Hospital, the Cerebral Palsy Center of St. John's Hospital, Springfield, Ill., and in private practice.

The distribution of cases according to diagnosis and the results obtained are indicated in the accompanying table.

Effects of Administration of Tridione to 47 Patients with Various Neurologic Diseases

	Number of Patients	Benefit	
		Considerable	Slight or None
Epilepsy			
With organic cerebral disease			
Grand mal	5	1	4
Petit mal	1	0	1
Both grand and petit mal	5	0	5
Total	11	1	10
Idiopathic epilepsy			
Grand mal	5	4	1
Petit mal	6	5	1
Both grand and petit mal	1	0	1
Total	12	9	3
Cerebral palsy			
Spastic	3	1	2
Athetoid	7	7	0
Dystonia musculorum	2	0	2
Total	12	8	4
Behavior disturbance	6	5	1
Tetanus	4	2	2
Chorea	2	0	2

Epilepsy.—Electroencephalographic studies on many of these patients before and after administration of Tridione showed improvement in the tracings after the administration of Tridione, in general paralleling the clinical response. From the table it is seen that when there is definite organic disease of the brain Tridione is of little, or no, benefit. When the symptoms are on an idiopathic basis, Tridione seems to be of considerable

value, or at least the equal of diphenylhydantoin and phenobarbital. Its greatest value was noted in the petit mal types, in which diphenylhydantoin and phenobarbital often aggravate the condition.

Cerebral Palsy.—In this series, 12 children with cerebral palsy were given Tridione for relaxation prior to institution of physical therapy. The greatest benefit was noted in patients with the athetoid form. All 7 children showed a considerable degree of relaxation. The spastic patients did not respond to the drug. Of the 2 patients with dystonia, 1 had a congenital condition and responded slightly to treatment, and in the other, with the acquired form, the drug aggravated the symptoms.

Thus the drug seems to be of benefit in producing relaxation of the tension of the athetoid type but fails to have any effect on the spastic form.

Functional Disturbances.—In this series, 4 patients presented serious behavior disturbances, such as stealing, running away from home and committing arson. All showed pronounced improvement with Tridione. One patient, who was included in the epilepsy group, had grand mal seizures which were controlled with diphenylhydantoin, and the behavior disturbance was effectively treated with a single daily dose of 10 grains (0.65 Gm.) of Tridione.

Chorea.—Two patients with chorea were treated with Tridione, with equivocal results. It was felt that the drug was of no greater value than phenobarbital.

Tetanus.—Four patients with tetanus were treated, 2 children and 2 adults. The drug was administered intravenously in 1 Gm. doses, with the object of stopping convulsions and spasms. The 2 adults had severe alcoholism, and although Tridione was effective in stopping the spasms, its action was only transitory. In the 2 children the drug was effective in controlling the convulsions. However, 1 child was in a terminal state on admission and died within twenty-four hours. The other child recovered.

Conclusions.—A new drug, Tridione, is reported, the action of which seems to be greatest in controlling those symptoms, convulsive or otherwise, in which the pyramidal tracts are not involved.

In treatment of convulsions due to organic disease of the brain or of cerebral palsy due to involvement of the pyramidal tract or its cells of origin, Tridione seems to be of some value, although not as much so as phenobarbital or diphenylhydantoin.

In treatment of convulsions of idiopathic origin, disturbances of behavior or cerebral palsy in cases in which the lesion is presumably extrapyramidal, the drug is of definite value. In management of petit mal the drug is of greater benefit than other drugs hitherto used.

In treatment of chorea the drug is of no value.

In treatment of tetanus it shows definite promise, and further investigation should be made.

Tridione has a low toxicity and is well tolerated in massive doses by both children and adults over a relatively long period. No side effects were noted in this series. The doses used varied from 5 to 10 grains (0.325 to 0.65 Gm.) three to four times daily.

DISCUSSION

DR. F. A. GIBBS: The authors of this exceedingly interesting paper have shown that Tridione has practical therapeutic value. When it was found that certain persons did not respond to large doses of phenobarbital or diphenylhydantoin, alone or in combination, I am sure many of us concerned with the investigation of epilepsy felt that we were at the end of our rope. This new drug offers new possibilities. The fact that it is not particularly valuable in cases of organic damage to the brain is not a serious limitation to its usefulness, for the great bulk of epileptic patients are without evidence of organic cerebral damage; nor is the statement that it is better for petit mal than for grand mal a serious disparagement. Petit mal can be extremely incapacitating, particularly with patients who drop to the ground with each attack or in whom the attacks come so close together that the condition can be referred to as petit mal status. The best anticonvulsant available, diphenylhydantoin, is not only relatively ineffective against petit mal but in many cases exacerbates it. I have had patients ask to be taken off treatment with diphenylhydantoin because they would rather be unconscious for a few minutes once a month with grand mal than unconscious all the time, i. e., be in petit mal status. If Tridione can be used to control petit mal, either alone or in combination with other drugs, it will be an exceedingly valuable remedy.

Dr. Perlstein has indicated that this is a preliminary report, and the electroencephalographic phase of the study was not supposed to be of major importance, the question at issue being whether Tridione does or does not have a therapeutic effect on clinical epilepsy. However, the authors are wise to have classified their cases, both clinically and electroencephalographically, in an effort to determine whether the drug has more value for one type of disease than another; and I agree that there is also advantage to be derived from knowing whether the drug entirely corrects the underlying cerebral dysrhythmia or merely prevents the most severe paroxysms of dysrhythmia, which externalize themselves in clinically obvious seizures.

DR. CLARENCE NEYMANN: I should like to ask about the measurement of the electrical currents. No doubt the authors know that the amount of current depends on the voltage times the amperage divided by the resistance. It is known that Ohm's law does not apply to organic substances and that in living organic substances the resistance decreases as the current continues to pass through the tissues. The currents employed were much more intense than those ordinarily used therapeutically. I should like to ask whether this was the intent of the experiment and whether the ohms of resistance were observed after the shock; also I should like to inquire of Dr. Perlstein whether the drug has been tried in cases of paralysis agitans following lethargic encephalitis.

DR. R. K. RICHARDS: As I tried to point out, these experiments were rather crude. The inductorium voltages were calibrated by a competent physicist. The current source was always the same, a 2 volt dry cell. The period of stimulation was probably too long. Further electroshock studies are being made with more refined technics, but I do not have the complete reports at this time. No particular significance is attached to the absolute voltage values. The important point is the sharp increase in threshold obtained after administering the drug.

DR. M. A. PERLSTEIN: This material is unquestionably overweighted with cases of convulsions due to organic disease of the brain because of the children seen in Cook County Hospital Children's Neurology Clinic there are many with lead poisoning, postinfectious encephalitis, head trauma and other organic conditions of the brain which result in recurrent convulsions. As pointed out by Dr. Gibbs, in most clinics devoted to epilepsy the number of cases of the idiopathic form would undoubtedly be higher.

I have not had any cases of paralysis agitans in this series, but many of the behavior conditions in children were postencephalitic, and this might indicate the possibilities of the drug in treatment of paralysis agitans.

ALEX J. ARIEFF, M.D., *Vice President, in the Chair*

Regular Meeting, Feb. 13, 1945

Serous Meningitis. DR. H. C. VORIS.

There is a heterogeneous group of patients who show evidence of increased intracranial pressure but who prove not to have a space-occupying lesion. Some of these patients have a history of infection contiguous to the intracranial cavity, in the ear, mastoid or sinuses. They are suspected of having a cerebral abscess. A few have had an injury to the head and are thought to have a subdural hematoma. Others have no history of infection or injury and are considered to have a brain tumor.

Six cases were presented in some detail to illustrate some of the problems encountered in cases of a condition which can be briefly described as characterized by subjective symptoms suggesting increased intracranial pressure and papilledema. Neurologic signs, exclusive of those associated with increased intracranial pressure, are minimal, and definite localization is seldom suggested. Other types of cases were briefly discussed, and a classification was indicated.

The author reported 43 personal cases in which intracranial exploration revealed no neoplasm or abscess and the diagnosis of serous meningitis or its equivalent had been made. The lack of adequate pathologic study in this series, as well as in most of the series reported, was mentioned. This absence of pathologic data is partly explained by the difficulty of getting adequate biopsy material at operation. The need for further microscopic studies in cases of serous arachnoiditis was emphasized.

DISCUSSION

DR. PAUL C. BUCY: This interesting group of cases is uniform only in the confusion they cause members of the medical profession. Certainly, there is a variety of causes which produce this general picture. One or two might be added to the list Dr. Voris presents. In many cases of aural infection thrombosis of the lateral sinus or of the veins of the cerebral cortex produces pressure similar to this. Often, when there is evidence of localized cerebral involvement, differentiation from cerebral abscess may be most difficult.

I have previously pointed out to members of this society that lead poisoning may also give rise to this picture of increased intracranial pressure. In 1 of the cases presented by Dr. Voris I believe the lateral roentgenogram of the skull gives a clue to the pathologic process. It will be noted that the attachment of the tentorium is pushed up higher than normal. This appearance is indicative of congenital atresia of the foramens of Magendie and Luschka. At operation one finds pronounced dilatation of the fourth ventricle, as Dr. Voris did in this case. The tentorium is curved upward in the center, and thus the occipital horns of the lateral ventricles, which lie laterally, are visible below the level of the central portion of the tentorium. Such displacement of the tentorium occurs only when the atresia of the foramens of the fourth ventricle is congenital.

DR. FREDERICK HILLER: Why do the symptoms sometimes appear so late if the atresia is congenital?

DR. PAUL C. BUCY: I wish I knew why this is so. I have seen atresia of the aqueduct give rise to increased intracranial pressure in the teen age group. This patient was 14 years old. I presume it is because the occlusion is not complete.

DR. HAROLD C. VORIS: Dr. Bucy's suggestion regarding the case I have reported as an instance of arachnoiditis of the posterior cistern is very interesting. Unfortunately, I did not take a biopsy specimen of the arachnoid at the first operation, so that the clinical diagnosis of arachnoiditis remains unverified.

Anatomic Contribution to the Problems of Perception, Awareness and Attention. DR. ADOLF WALLENBERG (by invitation).

The Electroencephalographic Pattern of Encephalitis. DR. F. A. GIBBS and MRS. E. L. GIBBS (by invitation).

Six channel electroencephalograms have been obtained in 133 cases of encephalitis of undetermined and specific types. In some cases single studies were made, and in others repeated examinations were carried out at varying intervals. In the acute phase a high degree of electroencephalographic abnormality is almost invariably present, even though the clinical symptoms are only moderately severe. In the subacute phase less extreme forms of abnormality occur; and, as might be expected, seizure discharges are commoner in persons who have seizures than in those who have not; the latter group shows a relatively high incidence of normal electroencephalograms. In the postencephalitic phase the electroencephalogram shows seizure discharges and exceedingly slow activity in persons in whom seizures have developed. Other patients, even those with severe paralysis agitans or oculogyric crises, usually have normal electroencephalograms. Epilepsy is a much commoner sequel of encephalitis in children than in adults. Postencephalitic epilepsy is much commoner in children than in adults. That such a condition is not misdiagnosed as idiopathic epilepsy is indicated by the fact that electroencephalograms of persons with this type of epilepsy usually show focal abnormalities, whereas the electroencephalograms of persons with idiopathic epilepsy do not.

DISCUSSION

DR. CHESTER DARROW: I should like to express appreciation of Dr. Gibbs's clear presentation and to ask whether he has observed any differential characteristic of so-called postencephalitic behavior. My associates and I have been particularly interested in this problem.

DR. A. EARL WALKER: How accurately can one prophesy from the electroencephalogram whether or not a patient with the acute stage of encephalitis will later have epileptic attacks?

DR. PAUL C. BUCY: I should like to ask whether it is possible to differentiate the slow waves seen in the case of encephalitis from those seen in the case of cerebral neoplasms, without regard, of course, to the progressive changes seen in successive electroencephalograms.

DR. F. A. GIBBS: Dr. Darrow asks about the incidence of electroencephalographic abnormality in children with behavior problems. When there is evidence of epilepsy, encephalitis or organic damage to the brain, the incidence of electroencephalographic abnormality is high. When this is absent and the behavior disorder itself is not of an epileptic, postencephalitic or organic type, the incidence of electroencephalographic abnormality is no higher than that in the control group.

Dr. Walker's question should be answered in the negative; in the acute phase it is impossible to say who is and who is not going to have epilepsy.

Dr. Bucy has asked about the specificity of the electroencephalogram for a particular type of lesion. It has

almost no specificity, but in certain cases tumor can be ruled out because the abnormality steadily increases, or decreases in one spot and increases in another.

PHILADELPHIA NEUROLOGICAL SOCIETY

GEORGE D. GAMMON, M.D., *Presiding*
Regular Meeting, Jan. 26, 1945

Surgical Treatment of Spontaneous Nontraumatic Hematoma of the Left Temporal Lobe: Report of Three Cases. DR. MICHAEL SCOTT.

Three cases of spontaneous hematoma of the left temporal lobe were reported in which the following syndrome was present: sudden onset with severe headache or aphasia; progressive drowsiness, and focal signs of involvement of the left temporal lobe, namely, (*a*) mixed aphasia with anomia and jargon speech, (*b*) right homonymous hemianopsia, (*c*) increased tendon reflexes on the right, (*d*) Hoffmann and Babinski signs on the right, (*e*) progressive weakness of the right side of the body, (*f*) absence of sensory disturbance and (*g*) shift of the pineal gland to the right. The spinal fluid pressure was usually increased, and the fluid was blood tinged, clear or xanthochromic. The total protein was always higher than normal.

An exploratory craniotomy on the left side revealed a subcortical hematoma in the posterior superior portion of the temporal lobe on the same side in all 3 cases. The clot was removed by suction, the dura closed and the bone flap replaced. Recovery with improvement took place in all 3 cases.

A series of 12 similar cases reported by various authors was reviewed. The symptoms in these cases fell into the same pattern as that just described. No definite etiologic factor could be found. Excitement and overexertion appeared to be the precipitating factors. In most cases studies concerned with exogenous toxins, blood dyscrasias and virus and other forms of infections were inadequate.

Conclusions.—Intracerebral hematoma of the left temporal lobe gives rise to a syndrome characteristic of an acute focal expanding intracranial lesion.

This condition is often erroneously diagnosed as a "stroke" resulting from cerebral arteriosclerosis or hypertension.

Exploratory craniotomy with evacuation of the blood clot offers the best method of treatment in cases showing progression of focal signs anl increased intracranial pressure.

DISCUSSION

DR. ANTHONY S. TORNAY: I had the opportunity of seeing the second patient presented by Dr. Scott. I first saw her several days after her admission to the hospital, and I made the clinical diagnosis of spontaneous subarachnoid hemorrhage. Later the first evidence of elevation of the optic disk was noted, and I suggested the possibility of a neoplasm into which a hemorrhage had taken place. Dr. Scott was asked to see the patient. I was much surprised and pleased with the results of his examination. After the patient came back from the surgical department, she complained of considerable headache. As days passed, she did not seem to be doing well. She was placed on a dry diet, and several spinal taps were made. I thought a second operation might have to be done. However, her husband solved the problem by removing her from the hospital; so I don't know what eventually happened. I did not diagnose the condition accurately. This presentation brings to the attention of the society the fact that such a condition may exist and that one should be mindful of it.

DR. SHERMAN F. GILPIN: It seems to me that the important thing is the making of the correct diagnosis. In case 1 I thought only of a vascular accident; when the roentgenogram showed a shift of the pineal gland, I did not think of an intracerebral clot. In another case there was choking of the disk. I do not remember the special feature of the third case, but something took all these cases out of the ordinary run of cases of vascular accidents. I am wondering whether there are not other cases which are unrecognized because there does not happen to be a choked disk or a shift of the pineal gland.

I cannot resist commenting on another point, although it is not particularly apropos, and that is the total protein values of the spinal fluid. These values have been interesting and and troubling me for some time. They were discussed at the meeting of the American Neurological Association this summer. I think it was a medical man who reported on observations on the spinal fluid in 100 normal subjects. A large percentage of these persons showed an increase of total proteins, and they had no indication of the presence of any neurologic disease. This certainly makes one wonder what significance one may attach to these elevated protein values.

DR. NATHAN S. SCHLEZINGER: In view of the apparent rarity of the condition, of which Dr. Scott found only 14 cases reported in the literature, I think another case ought to be recorded. A woman aged 22 was admitted to the Jefferson Hospital in May 1943. This patient presented the same condition as that described here except that her lesion was on the right side of the brain. The onset was acute, and typical of subarachnoid hemorrhage; in addition, there was complete left hemiplegia. The eyegrounds were normal. The spinal fluid pressure was increased to about 300 mm. in the early stage. About ten days after the onset the patient began to have headaches. In the meantime she had mental confusion, but this cleared up. She complained of severe headaches. The eyegrounds began to show papilledema, which increased to a level of about 4 D. within three weeks after the onset. The spinal fluid pressure reached 660 mm.; a liquid hematoma was removed at operation. Subsequently, there was a gradual and rather notable improvement, so that now, approximately two years after the onset, the patient is able to carry on a fairly normal life, including dancing. This patient was 22 years old; I do not know the average age in the cases reported. This case differs from the 3 cases reported by Dr. Scott in that the right side of the brain was affected.

DR. GEORGE D. GAMMON: Is the location of these hemorrhages particularly characteristic, and do they differ in any way from other cerebral hemorrhages? If not, what are the indications for operative treatment of intracerebral hemorrhage?

DR. MICHAEL SCOTT: I shall answer Dr. Gammon's question first. In all these cases a similar part of the temporal lobe was involved, as shown by the position of the silver clips in the postoperative roentgenograms. Naffziger, in a discussion on a paper by Craig and Adson, pointed out that in his experience both the traumatic and the spontaneous hematomas had a predilection for this portion of the temporal lobe.

The indication for operation is a progressive increase in intracranial pressure and focal signs. The patient has his initial symptoms, gets better for a while and then suddenly begins to grow worse, with severe headaches and signs of persistent increase in intracranial pressure and paralysis.

I was glad to hear the discussion concerning what would happen if these patients were not operated on. There are cases of intracerebral hemorrhage in which bleeding stops, the symptoms gradually abate, the clot becomes cystic and an intracerebral scar results. On the other hand, when there is definite evidence of progressive increase in focal signs, intracranial pressure and choked disk, I feel that one is justified in making an exploration. I see no reason that calcium should not be deposited in these areas of hemorrhage months or years after its occurrence. It was not seen or reported in the 15 cases reviewed tonight.

Dr. Gilpin's point about the relative importance of the pineal gland as a diagnostic aid is a pertinent one, because in many persons the pineal gland is not calcified. It was not calcified in the second case of this series. Of the 12 cases of hematoma in the left temporal lobe which were reported in the literature, a roentgenogram of the skull was mentioned in only 1, and that was reported as normal. In 2 cases air studies were made. One cannot deny the diagnostic value of a shift of the pineal gland when it is over 3 mm. The paper read tonight was restricted to hematomas of the left temporal lobe. I must emphasize that these hemorrhages may occur in any other lobe and may give rise to focal symptoms characteristic of that area.

Book Reviews

Textbook of Neuropathology. Second edition. By Arthur Weil, M.D. Price, $5. Pp. 356. New York: Grune & Stratton, Inc., 1945.

In his preface to the second edition of this textbook, the author admits that while great strides have been made in neuropsychiatry, especially therapeutically, since he published his first edition, neuropathology as such has not been affected by these discoveries. He feels that "most of the contributions to neuropathology have been made in the experimental field; the investigation of the vitamin deficiencies, the experimental production of tumors of nervous tissues, and the experimental study of the pathology of the different shock treatments." It is therefore to these newer additions that the reader turns his attention, only to discover that in the whole book of 356 pages, 5 to 10 pages at most are devoted to the newer works referred to by the author. The material dealing with vitamin deficiencies and shock treatments is rather abbreviated. The data dealing with the experimental production of tumors are presented in somewhat more detail, perhaps because the author has been very active in this field of study. For that matter, his well known interest in the chemistry of the nervous system makes itself evident throughout the book, and from that angle the work presents a departure in orientation from the usual textbooks of neuropathology.

The book as a whole is readable, although in some spots it falls prey to the nemesis of most textbooks—that is the listing off in the text proper of works by other authors, without elaboration. There is, however, a minimum of this, and at the end of the book is a fairly good bibliography, arranged according to subject matter, for those who are interested in further reading. The author reveals here and there a freedom of thinking which tries to break through the fetters of classic and conventional neuropathology, but he ruefully admits that he is limited by the confines of his subject, especially as far as classification is concerned.

One criticism which could be leveled at this book, as well as at pathologic texts in general, is that whereas many of the pictures may mean something to the pathologist, unless there is a complete legend, with specific designation of the exact areas referred to, they usually represent a meaningless splotch to the young clinician.

In the main, this book is satisfactory and should meet the needs of the practicing neurologist.

The Falling Sickness: A History of Epilepsy from the Greeks to the Beginnings of Modern Neurology. By Owsei Temkin. Price $4. Pp. 324, with index and illustrations. Baltimore: Johns Hopkins Press, 1945.

In grasping and dealing with difficult concepts, a consideration of their history is a great, sometimes an essential, aid. For the first time, a scholarly, definitive history of the development of knowledge of epilepsy is made available, and every student of the subject should read it with care. In a work bristling with references and verbatim quotations, Dr. Temkin leads his readers from fragmentary references to convulsions in the literature of antiquity to a careful study of the philosophic and physiologic theories of Jackson and Charcot.

Many interesting bits of information are to be gathered on the way. The reference to epilepsy in the Code of Hammurabi is vague and of questionable authenticity. Unilateral seizures were mentioned by Hippocrates and were well described by Aretaeus, who stated that they could sometimes be controlled by sensory stimulation of the affected part. Hippocrates referred to epilepsy at one point as "the great disease," and this is apparently the origin of the term "grand mal." Aristotle first called attention to the incidence of epilepsy among distinguished characters of history. Galen coined the term "aura," because one of his patients complained of a feeling like a breeze blowing on one extremity before loss of consciousness occurred. Galen further made a distinction between epilepsy due to an idiopathic disease of the brain and that due to "sympathetic" involvement, secondary to disease elsewhere in the body.

The confusion between the disease epilepsy and, first, witchcraft and, later, hysteria and a fantastic empiric polypharmacy beclouded the entire subject from the time of the giants of antiquity to the nineteenth century. Dr. Temkin's account of the development of modern conceptions is far too complicated and detailed to permit abstraction.

Dr. Temkin accepts the diagnosis of epilepsy for Julius Caesar, Caligula, Petrarca, Charles V, Torquato and Mohammed. It is a matter of some regret that one does not have his opinion on the authenticity of the diagnosis for other distinguished men, for example, Napoleon and Peter the Great.

This volume was financed by the Epilepsy Medical Research Fund of Johns Hopkins University, and it constitutes a most important contribution to the subject.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. Second edition. By Frank R. Ford, M.D., Associate Professor of Neurology, Johns Hopkins University. Price, $12.50. Pp. 1143. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

This book is that comparative rarity, a definitive work in its field. The first edition gained wide recognition for its authority, and the new volume contains additional material on such topics, among many, as hemorrhagic disease of the newborn and disorders of lipid metabolism.

The first chapter is concerned with the examination of the nervous system, especially its modification in testing children. The various aids to neurologic diagnosis, such as roentgenography and electroencephalography, are also thoroughly described.

The vast bulk of the book is devoted to descriptions of the various neurologic syndromes and disease entities. Throughout, the style is lucid, the references are numerous and easily accessible and the illustrations frequent and enlightening.

One might wish for more material on certain psychiatric aspects of neurologic conditions, for example, the behavior disorders of children following head injury. But since such material is at the present time largely speculative and conjectural, one respects Dr. Ford's right to omit such discussions from his work.

The book is unqualifiedly and enthusiastically recommended to any one interested in the neurologic disorders of the young.

Distonia de torção. By A. Austregésilo Jr. Pp. 316, with 133 illustrations and bibliography. Rio de Janeiro: Irmãos di Giorgio & Cia, 1945.

This thesis, in the classic style, details personal observations in 5 cases and covers the literature in sketchy style. Most of the illustrations dealing with the pathologic anatomy, 47 from a single case, are unconvincing, while 20 additional photographs of a patient in various attitudes are too small to permit accurate analysis of the patterns of muscular activity. The case reports are padded with unessential information. It is doubtful whether the sixteen pages of references have been checked with the original articles. Aside from revealing the fact that dystonia occurs in Brazil, this monograph cannot be said to add much to knowledge of the subject. It is to be hoped that the author will break with tradition in his next volume and dig below the surface; the present work reflects no great credit on Brazilian neurology.

Egas Moniz: Ultima lição; bibliográfia. Pp. 86. Lisbon, Portugália, 1944.

This is the swan-song of Egas Moniz, who retired from the field of teaching in November 1944. It is a review of his work, an apology and an acknowledgment to those who have been associated with him. It is written in the elegant prose which the author has applied to other fields besides medicine. The bibliography includes 324 titles, including books on medical history, art, politics and geography, for Egas Moniz was an essayist and critic as well as a physician. The two major contributions of Egas Moniz are described, fortunately, in the first person. As he says, it is of special interest to readers to know what led up to the experiments and how the preliminary steps were made. Egas Moniz gives much more space to his work with cerebral angiography than he does to prefrontal leukotomy. In making his farewell, he looks forward to the changes that will come about in the field of medicine and leaves that field to younger men.

Character-Analysis: Principles and Technique for Psychoanalysts in Practice and in Training. By Wilhelm Reich, M.D. Translated by Theodore P. Wolfe. Second edition. Price, $4.50. Pp. 324. New York: Orgone Institute Press, Inc., 1945.

As the subtitle indicates, the book is of primary interest to psychoanalysts. It is an excellent study of the problems of technic. Reich's exposition of his thesis is clear and penetrating. Much of the material on character analysis is part and parcel of present day analytic procedure. The discussions of the many problems that arise in psychoanalytic practice are clear and instructive. His account of the differences between neurotic symptoms and character problems is clear and cogent. The author stresses the need of knowledge about the orgasm and its psychic function. His disagreement with Freud's concept of the death instinct as an explanation of masochism is presented. His own theoretic conception of the origin of masochism is well stated.

The footnotes relate to Reich's more recent work with the Orgone, but they can be easily disregarded by the reader. They merely intensify one's regret that so able a worker wanders so far from scientific studies of human behavior.

Mental Disorders in Later Life. Edited by Oscar J. Kaplan, Ph.D. Price, $5. Pp. 436. Stanford University, Calif.: Stanford University Press, 1945.

The fact that more people are continuing to live into old age is of great importance to psychiatry, as well as to general medicine. It is necessary to reevaluate the knowledge that exists concerning the factors bearing on the mental health and mental disease of this older age group. In general medicine, as well as in psychiatry, there have been too long a fatalistic attitude toward the ills of the aged and a lack of therapeutic initiative.

This volume contains a compilation to date of the knowledge concerning the mental disturbances of the elderly and some of the physical and emotional factors involved in producing them. The chapter on the physiologic aspects of mental disorders in later life, by Nathan W. Shock, is particularly good. He concludes that there is in the aged a progressive loss in the homeostatic capacities of the organism. It is true that in old people hemostasis is often maintained, but only by utilizing reserve mechanisms. It is pointed out that research is needed in determining the amount of "physiologic stress" required to bring out these secondary mechanisms.

There is a good evaluation of the psychologic characteristics of aging and of the aged and the role these factors play in mental disorder. The sociologic aspects of the aged are reviewed, and the immensity of the problem is pointed out. There are totally inadequate cultural institutions for taking into consideration the needs, both physical and emotional, of old people. For proper mental hygiene and preventive psychiatry these aspects must be thoroughly explored.

The fact that neuroses in old people have a greater incidence than the psychoses is not generally appreciated. Certainly, much is written about the psychoses and too little about the neuroses of later life. Norman Cameron discusses these neuroses rather comprehensively and indicates patterns of therapy.

There are, of course, several chapters concerned with the involutional psychoses, the presenile dementias, the senile psychoses and the psychoses associated with cerebral arteriosclerosis. Psychosomatic medicine, psychotherapy and mental hygiene with reference to the older patient are given space in this compendium. The material is presented clearly, simply and interestingly. Some chapters have an extensive bibliography, and in some there is an attempt to indicate where more research is needed.

This volume is recommended for use of all psychiatrists.